STIC Search Report
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STIC Database Tracking Number: 179586

TO: Alton Pryor
Location: REM 4A39/4C70
Art Unit: 1616
February 14, 2006

Case Serial Number: 09/328742

From: P. Sheppard
Location: Remsen Building
Phone: (571) 272-2529

sheppard@uspto.gov

Search Notes

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Scientific and Technical Information Center

SEARCH REQUEST FORM

Requester's Full Name: Alton Pryor Examiner #: 74458 Date: 2/8/06
Art Unit: 1616 Phone Number: 2-0621 Serial Number: 09/328,742
Location (Bldg/Room#): REM4B39 (Mailbox #): 4THFL Results Format Preferred (circle): PAPER DISK
****

To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Title of Invention: _____

Inventors (please provide full names): _____

_____

Earliest Priority Date: _____

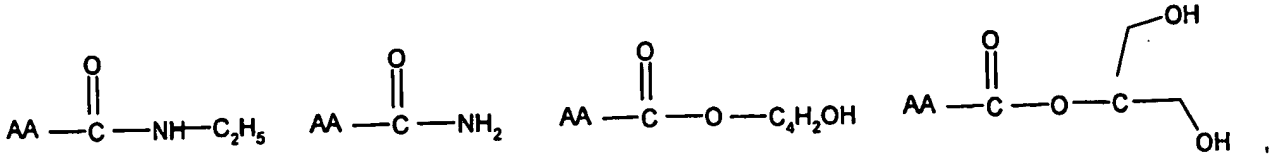
Search Topic:
Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known.

For Sequence Searches Only ***Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.***

Search claim 27 and 28

Appl. No.: 09/328,742
Response to Office communication dated: 5/24/2005
Attorney Docket: UCONAP/141/US

28. (new) A method of inhibiting transport of anandamide in an individual or animal comprising administering to the individual or animal a therapeutically effective amount of a compound represented by the following structural formula and physiologically acceptable salts thereof



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

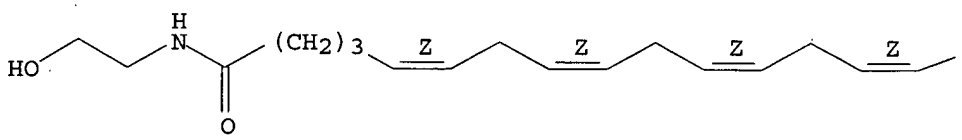
L19 ANSWER 13 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:550217 HCAPLUS
DOCUMENT NUMBER: 127:246072
TITLE: Functional role of high-affinity **anandamide transport**, as revealed by selective inhibition
AUTHOR(S): Beltramo, M.; Stella, N.; Calignano, A.; Lin, S. Y.; Makriyannis, A.; Piomelli, D.
CORPORATE SOURCE: The Neurosciences Inst., San Diego, CA, 92121, USA
SOURCE: Science (Washington, D. C.) (**1997**), 277(5329), 1094-1097
CODEN: SCIEAS; ISSN: 0036-8075
PUBLISHER: American Association for the Advancement of Science
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Anandamide, an endogenous ligand for central cannabinoid receptors, is released from neurons on depolarization and rapidly inactivated. Anandamide inactivation is not completely understood, but it may occur by transport into cells or by enzymic hydrolysis. The compound N-(4-hydroxyphenyl)arachidonylamide (AM404) was shown to inhibit high-affinity anandamide accumulation in rat neurons and astrocytes in vitro, an indication that this accumulation resulted form carrier-mediated transport. Although AM404 did not activate cannabinoid receptors or inhibit anandamide hydrolysis, it enhanced receptor-mediated anandamide responses in vitro and in vivo. The data indicate that carrier-mediated transport may be essential for termination of the biol. effects of anandamide, and may represent a potential drug target.

IT **94421-68-8, Anandamide**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(carrier-mediated **transport** of **anandamide**)
RN 94421-68-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



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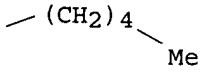


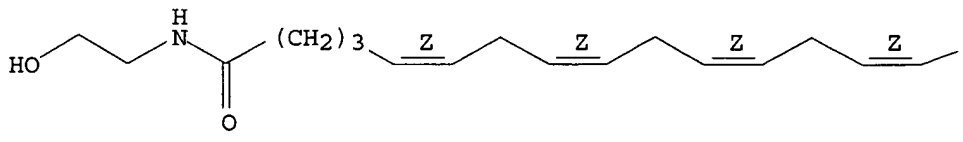
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 14 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN

CESSION NUMBER: 1997:495779 HCAPLUS
CUMENT NUMBER: 127:188622
TLE: Accumulation of N-arachidonoylethanolamine (anandamide) into cerebellar granule cells occurs via facilitated diffusion
AUTHOR(S): Hillard, Cecilia J.; Edgemond, William S.; Jarrahian, Abbas; Campbell, William B.
CORPORATE SOURCE: Department of Pharmacology and Toxicology, Medical College of Wisconsin, Milwaukee, WI, 53226, USA
SOURCE: Journal of Neurochemistry (**1997**), 69(2), 631-638
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Lippincott-Raven
DOCUMENT TYPE: Journal
LANGUAGE: English
AB N-Arachidonoylethanolamine (anandamide, AEA) is a putative endogenous ligand of the cannabinoid receptor. Intact cerebellar granule neurons in primary culture rapidly accumulate AEA. [3H]AEA accumulation by cerebellar granule cells is dependent on incubation time (t1/2 of 2.6 ± 0.8 min at 37°C) and temperature The accumulation of AEA is saturable and has an apparent Km of 41 ± 15 μM and a Vmax of 0.61 ± 0.04 nmol/min/106 cells. [3H]AEA,accumulation by cerebellar granule cells is significantly reduced by 200 μM phloretin (57.4 ± 4% of control) in a noncompetitive manner. [3H]AEA accumulation is not inhibited by either ouabain or removal of extracellular sodium. [3H]AEA accumulation is fairly selective for AEA among other naturally occurring N-acylethanolamines; only N-oleoylethanolamine significantly inhibited [3H]AEA accumulation at a concentration of 10 μM. The ethanolamides of palmitic acid and linolenic acid were inactive at 10 μM. N-Arachidonoylbenzylamine and N-arachidonoylpropylamine, but not arachidonic acid, 15-hydroxy-AEA, or 12-hydroxy-AEA, compete for AEA accumulation. When cells are preloaded with [3H]AEA, temperature-dependent efflux occurs with a half-life of 1.9 ± 1.0 min. Phloretin does not inhibit [3H]AEA efflux from cells. These results suggest that AEA is accumulated by cerebellar granule cells by a protein-mediated transport process that has the characteristics of facilitated diffusion.
IT **94421-68-8, Anandamide**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(accumulation of N-arachidonoylethanolamine into cerebellar granule cells occurs via facilitated diffusion)
RN 94421-68-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



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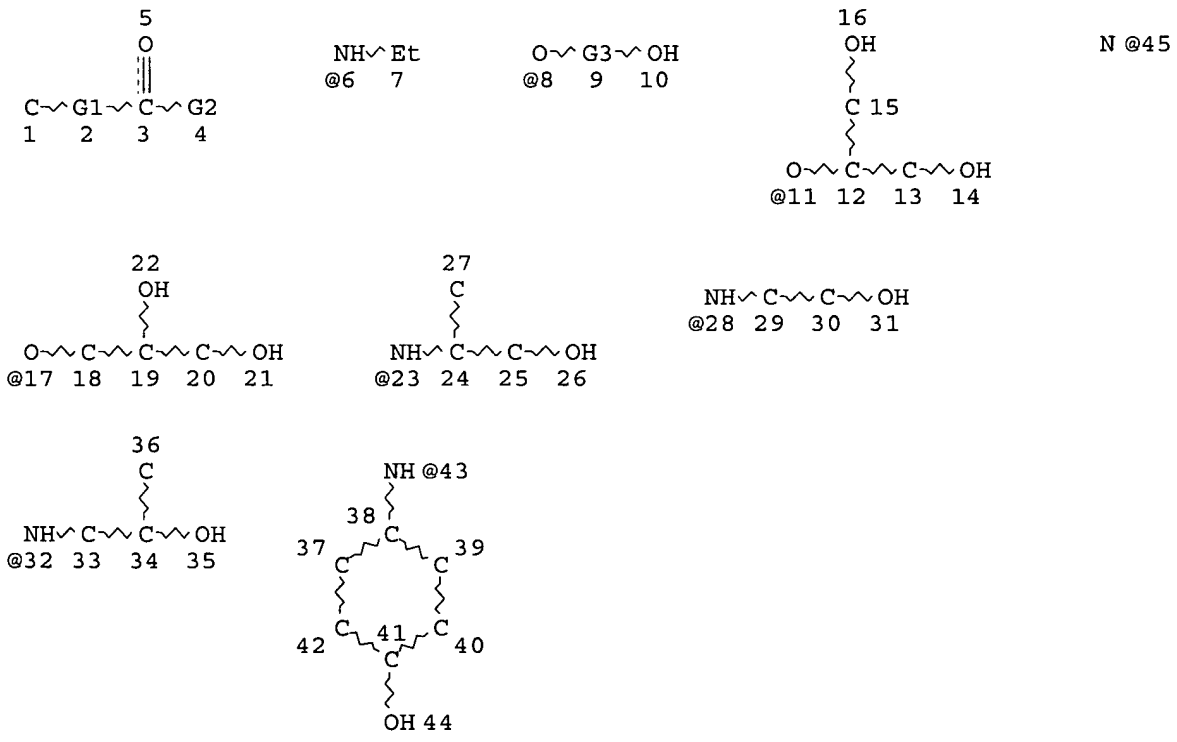

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Page 1-B
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REP G3=(4-4) C
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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 45

STEREO ATTRIBUTES: NONE
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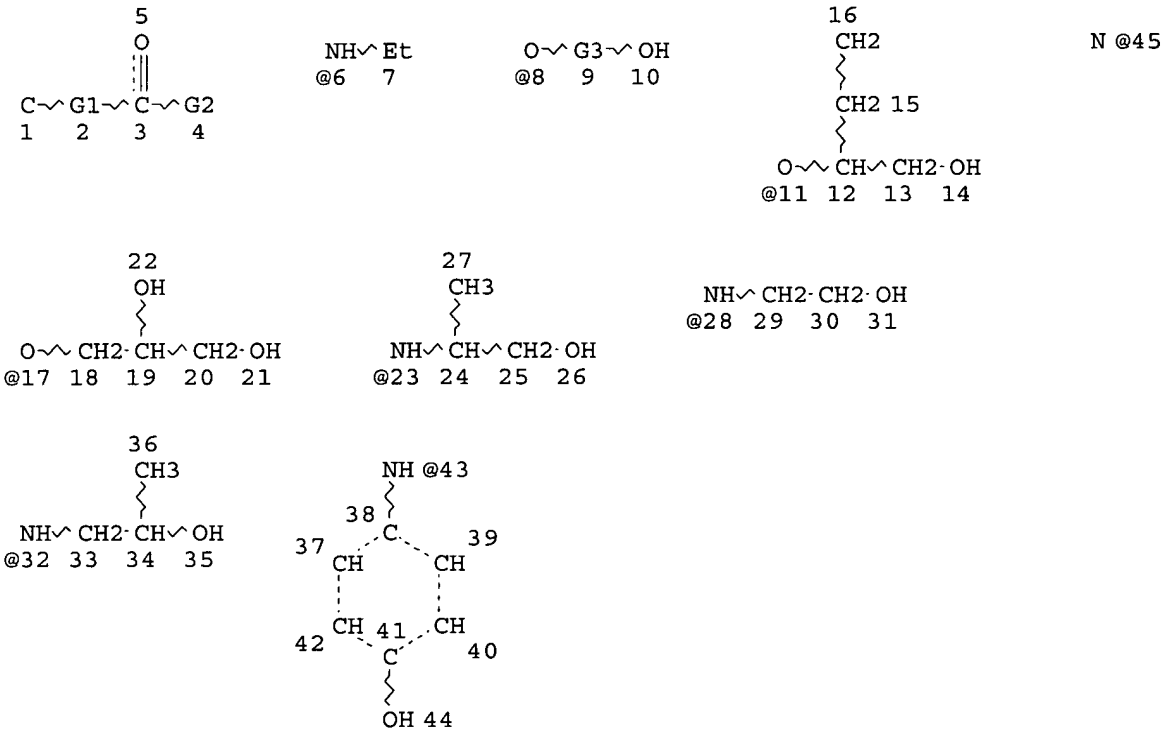
L3 STR



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DEFAULT MLEVEL IS ATOM
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NUMBER OF NODES IS 45

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L8          1727 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L6 OR ?ANANDAMIDE?
L10         1212 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7(L)L8
L17          133 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8(5A)TRANSPORT
L18          120 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L10 AND L17
L19           16 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L18 AND PD=<SEPTEMBER 20,
                 1999


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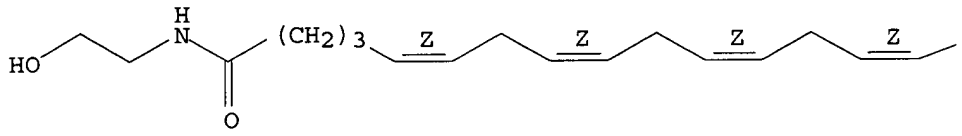
L19  ANSWER 1 OF 16  HCAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         1999:510255  HCAPLUS
DOCUMENT NUMBER:          131:295096
TITLE:                    Unsaturated Long-Chain N-Acyl-vanillyl-amides
                          (N-AVAMs): Vanilloid Receptor Ligands That Inhibit
                          Anandamide-Facilitated Transport and
                          Bind to CB1 Cannabinoid Receptors
AUTHOR(S):                Melck, Dominique; Bisogno, Tiziana; De Petrocellis,
                          Luciano; Chuang, Huai-hu; Julius, David; Bifulco,
                          Maurizio; Di Marzo, Vincenzo
CORPORATE SOURCE:         Istituto per la Chimica di Molecole di Interesse
                          Biologico, Consiglio Naz. Ric., Arco Felice, Napoli,
                          80072, Italy
SOURCE:                   Biochemical and Biophysical Research Communications (
                          1999), 262(1), 275-284
                          CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER:                Academic Press
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   We investigated the effect of changing the length and degree of unsatn. of
     the fatty acyl chain of N-(3-methoxy-4-hydroxy)-benzyl-cis-9-
     octadecenoamide (olvanil), a ligand of vanilloid receptors, on its
     capability to: (i) inhibit anandamide-facilitated
     transport into cells and enzymic hydrolysis, (ii) bind to CB1 and
     CB2 cannabinoid receptors, and (iii) activate the VR1 vanilloid receptor.
     Potent inhibition of [14C]anandamide accumulation into cells was achieved
     with C20:4 n-6, C18:3 n-6 and n-3, and C18:2 n-6 N-acyl-vanillyl-amides
     (N-AVAMs). The saturated analogs and Δ9-trans-olvanil were inactive.
     Activity in CB1 binding assays increased when increasing the number of
     cis-double bonds in a n-6 fatty acyl chain and, in saturated N-AVAMs, was not
     greatly sensitive to decreasing the chain length. The C20:4 n-6 analog
     (arvanil) was a potent inhibitor of anandamide accumulation (IC50 = 3.6
     μM) and was 4-fold more potent than anandamide on CB1 receptors (Ki =
     0.25-0.52 μM), whereas the C18:3 n-3 N-AVAM was more selective than
     arvanil for the uptake (IC50 = 8.0 μM) vs. CB1 receptors (Ki = 3.4
     μM). None of the compds. efficiently inhibited [14C]anandamide
     hydrolysis or bound to CB2 receptors. All N-AVAMs activated the cation
     currents coupled to VR1 receptors overexpressed in Xenopus oocytes. In a
     simple, intact cell model of both vanilloid- and anandamide-like activity,
     i.e., the inhibition of human breast cancer cell (HBCC) proliferation,
     arvanil was shown to behave as a "hybrid" activator of cannabinoid and
     vanilloid receptors. (c) 1999 Academic Press.
IT   94421-68-8, Anandamide
```

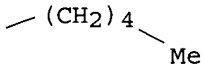
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(unsatd. long-chain N-acyl-vanillyl-amides as vanilloid receptor ligands that inhibit **anandamide**-facilitated **transport** and bind to CB1 cannabinoid receptors)
RN 94421-68-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 2 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:477642 HCAPLUS
DOCUMENT NUMBER: 131:251951
TITLE: Structure-activity relationships of anandamide, an endogenous cannabinoid ligand
AUTHOR(S): Khanolkar, Atmaram D.; Makriyannis, Alexandros
CORPORATE SOURCE: Departments of Pharmaceutical Sciences, University of Connecticut, Storrs, CT, 06269, USA
SOURCE: Life Sciences (**1999**), 65(6/7), 607-616
CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 45 refs. Identification of arachidonylethanolamide (anandamide) as an endogenous cannabinoid is one of the most important developments in cannabinoid research in recent years. In a relatively short period of time thereafter, pharmacol. and biochem. studies have confirmed initial speculations that anandamide is a neuromodulator and significantly advanced our understanding of cannabinoid biochem. Moreover, the discovery of anandamide has led to the identification of two heretofore unknown proteins associated with cannabinoid physiol.: (1)Anandamide Amidohydrolase (AAH), an enzyme responsible for the hydrolytic breakdown of anandamide and (2) the Anandamide Transporter (ANT), a carrier protein involved in the **transport** of **anandamide** across the cell membrane. Evidence obtained so far suggests that these two proteins, in combination, are responsible for the termination of the biol. actions of anandamide. Also, the discovery of anandamide has revealed a novel class of more selective cannabimimetic agents possessing a somewhat different pharmacol. profile of potential

therapeutic value. A number of such analogs have now been reported many of which possess markedly improved cannabinoid receptor affinity and metabolic stability compared to those of the parent ligand. Generally, anandamide and all known analogs exhibit significant selectivity for the CB1 receptor and modest to very low affinity for CB2. For this reason, this group of compds. can be considered as CB1 ligands. The purpose of this review is to summarize the structure-activity relationships (SAR) of anandamide for the CB1 cannabinoid receptor and to define the structural requirements for the substrates and the inhibitors of anandamide amidohydrolase and the anandamide transporter.

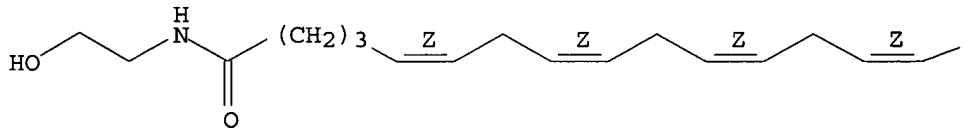
IT **94421-68-8**, **Anandamide**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(structure-activity relationships of **anandamide**, endogenous cannabinoid ligand)

RN 94421-68-8 HCAPLUS

CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



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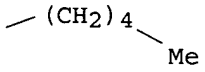

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L19 ANSWER 3 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:423969 HCAPLUS

DOCUMENT NUMBER: 131:194633

TITLE: Extrapyramidal and neuroendocrine effects of AM404, an inhibitor of the carrier-mediated **transport** of **anandamide**

AUTHOR(S): Gonzalez, S.; Romero, J.; De Miguel, R.; Lastres-Becker, I.; Villanua, M. A.; Makriyannis, A.; Ramos, J. A.; Fernandez-Ruiz, J. J.

CORPORATE SOURCE: Department of Biochemistry and Faculty of Medicine, Complutense University, Madrid, 28040, Spain

SOURCE: Life Sciences (**1999**), 65(3), 327-336
CODEN: LIFSAK; ISSN: 0024-3205

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A selective inhibitor of the carrier-mediated transport of endogenous cannabinoids, N-(4-hydroxyphenyl)-arachidonylethanolamide (AM404), has been recently synthesized and proposed as a useful tool for studying the physiol. effects of endogenous cannabinoids and as a potential therapeutic

agent in a variety of diseases. In the present study, we have examined the effects of this compound in two important brain processes in which a role for anandamide and other endogenous cannabinoids has been claimed: neuroendocrine regulation and extrapyramidal motor activity. A single and well-characterized dose of AM404, which presumably resulted in a significant elevation of the levels of endogenous cannabinoids, produced a marked decrease in plasma prolactin (PRL) levels, with no changes in LH levels. This decrease in PRL levels was accompanied by an increase in the activity of tyrosine hydroxylase (TH) in the medial basal hypothalamus. Both decreased PRL secretion and increased hypothalamic TH activity have been reported to occur after the administration of anandamide. Administration of AM404 also produced a marked motor inhibition in the open-field test, as also reported for anandamide, with a decrease in ambulatory and exploratory activities and an increase in the time spent in inactivity. This was accompanied by a decrease in the activity of TH in the substantia nigra, an effect also previously observed for anandamide.

IT **183718-77-6**, AM 404
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(extrapyramidal and neuroendocrine effects of AM404, an inhibitor of the carrier-mediated **transport** of **anandamide**)

RN 183718-77-6 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-(4-hydroxyphenyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

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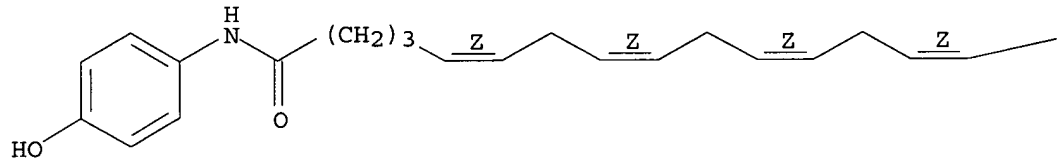
PAGE 1-A



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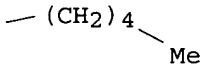

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 4 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:314488 HCAPLUS
DOCUMENT NUMBER: 131:100242
TITLE: Structural determinants for recognition and translocation by the anandamide transporter
AUTHOR(S): Piomelli, D.; Beltramo, M.; Glasnapp, S.; Lin, S. Y.; Goutopoulos, A.; Xie, Xiang-Qun; Makriyannis, A.
CORPORATE SOURCE: The Neurosciences Institute, San Diego, CA, 92121, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (**1999**), 96(10), 5802-5807
CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The biol. actions of anandamide (arachidonylethanolamide), an endogenous cannabinoid lipid, are terminated by a two-step inactivation process consisting of carrier-mediated uptake and intracellular hydrolysis. Anandamide uptake in neurons and astrocytes is mediated by a high-affinity, Na+-independent transporter that is selectively inhibited by N-(4-hydroxyphenyl)-arachidonamide (AM404). In the present study, we examined the structural determinants governing recognition and translocation of substrates by the anandamide transporter constitutively expressed in a human astrocytoma cell line. Competition expts. with a select group of analogs suggest that substrate recognition by the transporter is favored by a polar nonionizable head group of defined stereochem. configuration containing a hydroxyl moiety at its distal end. The secondary carboxamide group interacts favorably with the transporter, but may be replaced with either a tertiary amide or an ester, suggesting that it may serve as hydrogen acceptor. Thus, 2-arachidonylglycerol, a putative endogenous cannabinoid ester, also may serve as a substrate for the transporter. Substrate recognition requires the presence of at least one cis double bond situated at the middle of the fatty acid carbon chain, indicating a preference for ligands whose hydrophobic tail can adopt a bent U-shaped conformation. On the other hand, uptake expts. with radioactively labeled substrates show that no fewer than four cis nonconjugated double bonds are required for optimal translocation across the cell membrane, suggesting that substrates are transported in a folded hairpin conformation. These results outline the general structural requisites for **anandamide transport** and may assist in the development of selective inhibitors with potential clin. applications.

IT **111-57-9 111-58-0 35474-99-8**
85146-53-8 94421-68-8 150314-34-4
156910-28-0 157182-49-5 157182-50-8
162758-93-2 162758-96-5 164228-51-7
166100-34-1 183718-67-4 183718-77-6
187224-16-4 187224-18-6 231632-70-5
231632-76-1 231632-77-2
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(structural determinants for recognition and translocation by the **anandamide** transporter)

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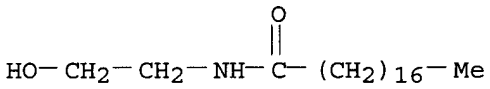

RN 111-58-0 HCAPLUS
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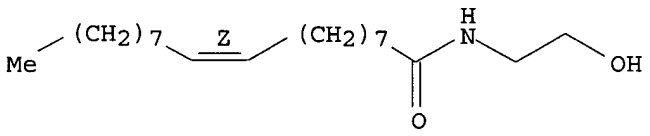
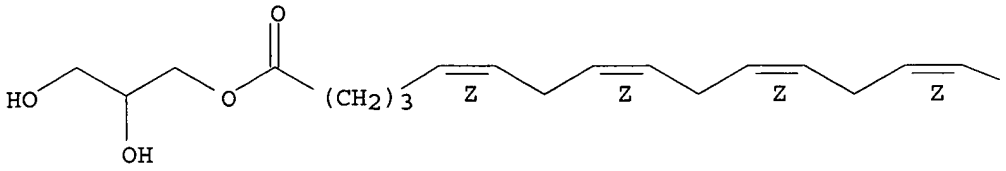


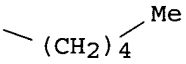
RN 35474-99-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenoic acid, 2,3-dihydroxypropyl ester, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A

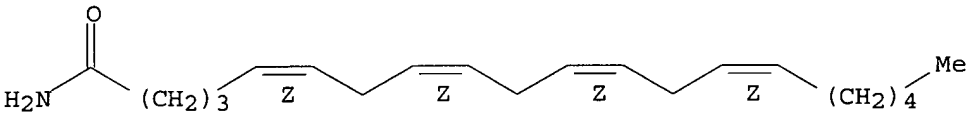


PAGE 1-B



RN 85146-53-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

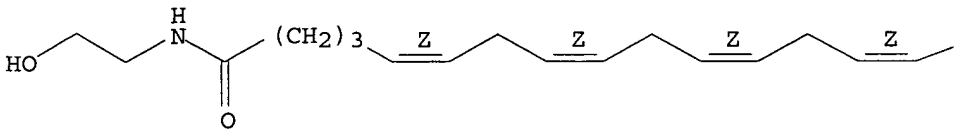
Double bond geometry as shown.



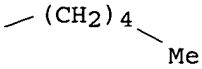
RN 94421-68-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



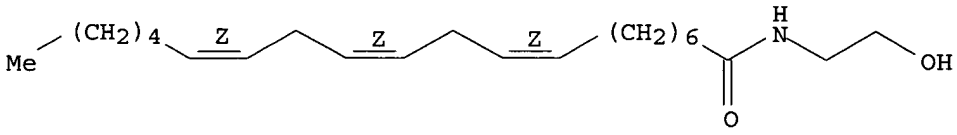
PAGE 1-B



RN 150314-34-4 HCAPLUS
CN 8,11,14-Eicosatrienamide, N-(2-hydroxyethyl)-, (8Z,11Z,14Z)- (9CI) (CA

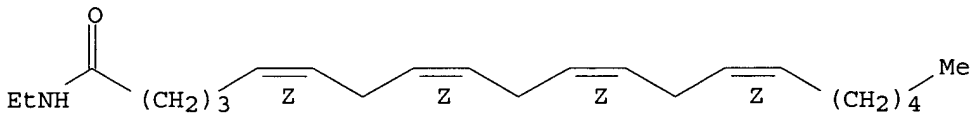
INDEX NAME)

Double bond geometry as shown.



RN 156910-28-0 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-ethyl-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

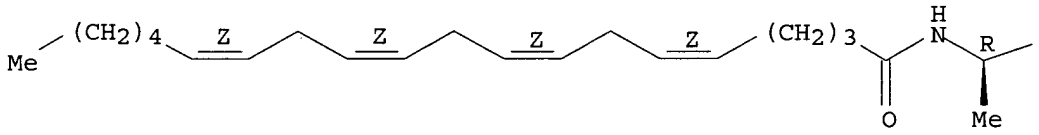
Double bond geometry as shown.



RN 157182-49-5 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-[(1R)-2-hydroxy-1-methylethyl]-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.

PAGE 1-A



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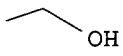
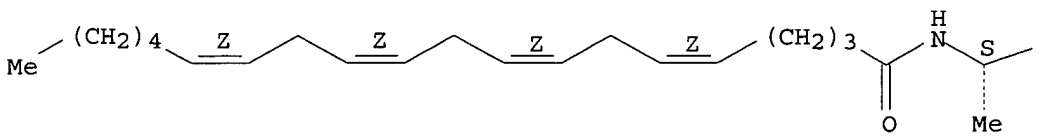


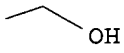
RN 157182-50-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-[(1S)-2-hydroxy-1-methylethyl]-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A

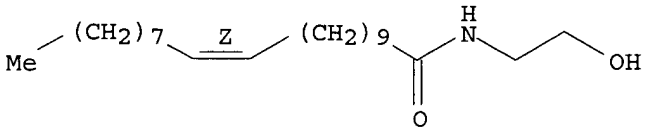


PAGE 1-B



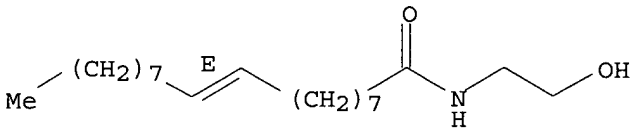
RN 162758-93-2 HCAPLUS
CN 11-Eicosenamide, N-(2-hydroxyethyl)-, (11Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 162758-96-5 HCAPLUS
CN 9-Octadecenamide, N-(2-hydroxyethyl)-, (9E)- (9CI) (CA INDEX NAME)

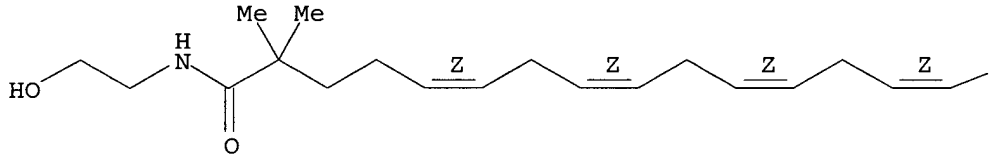
Double bond geometry as shown.



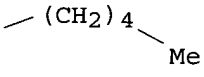
RN 164228-51-7 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-2,2-dimethyl-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A

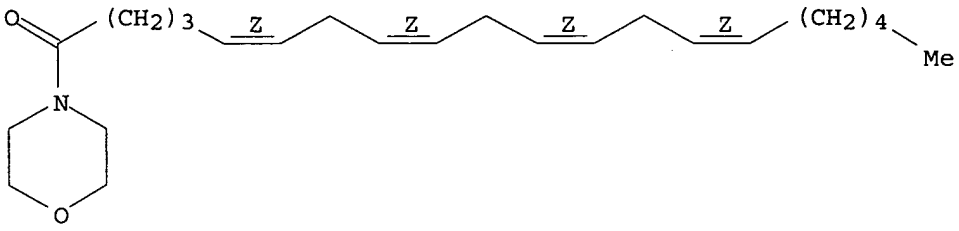


PAGE 1-B



RN 166100-34-1 HCAPLUS
CN Morpholine, 4-[(5Z,8Z,11Z,14Z)-1-oxo-5,8,11,14-eicosatetraenyl]- (9CI) (CA INDEX NAME)

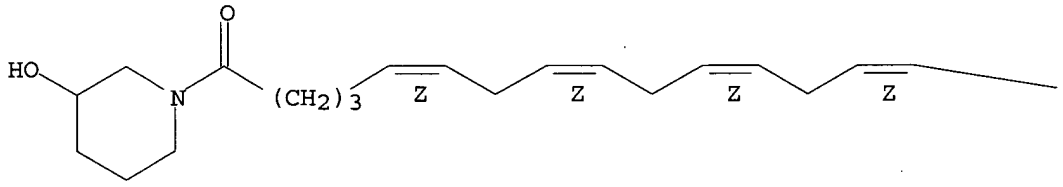
Double bond geometry as shown.



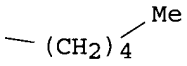
RN 183718-67-4 HCAPLUS
CN 3-Piperidinol, 1-[(5Z,8Z,11Z,14Z)-1-oxo-5,8,11,14-eicosatetraenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



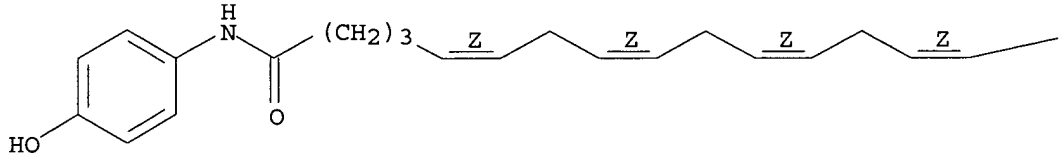
PAGE 1-B



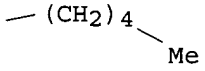
RN 183718-77-6 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-(4-hydroxyphenyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

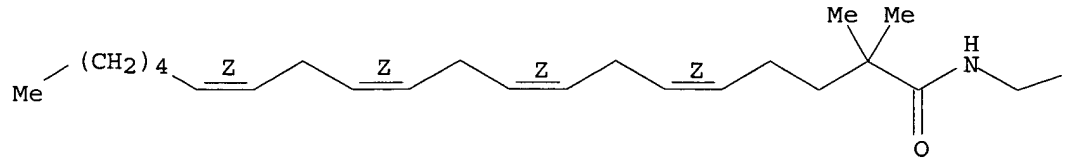


RN 187224-16-4 HCAPLUS

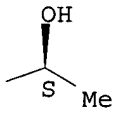
CN 5,8,11,14-Eicosatetraenamide, N-[(2S)-2-hydroxypropyl]-2,2-dimethyl-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.

PAGE 1-A



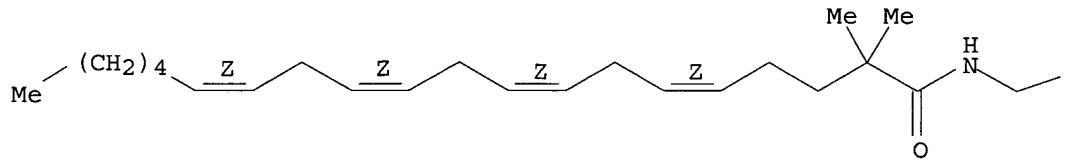
PAGE 1-B



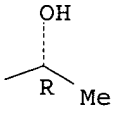
RN 187224-18-6 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-[(2R)-2-hydroxypropyl]-2,2-dimethyl-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

PAGE 1-A

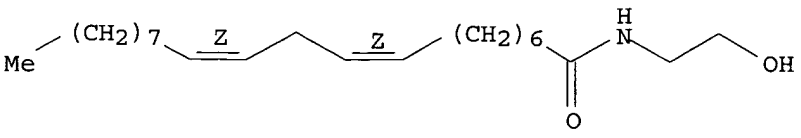


PAGE 1-B



RN 231632-70-5 HCAPLUS
CN 8,11-Eicosadienamide, N-(2-hydroxyethyl)-, (8Z,11Z)- (9CI) (CA INDEX NAME)

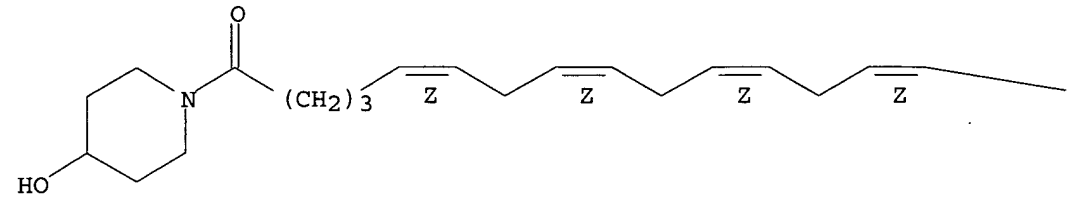
Double bond geometry as shown.



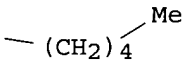
RN 231632-76-1 HCAPLUS
CN 4-Piperidinol, 1-[(5Z,8Z,11Z,14Z)-1-oxo-5,8,11,14-eicosatetraenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A

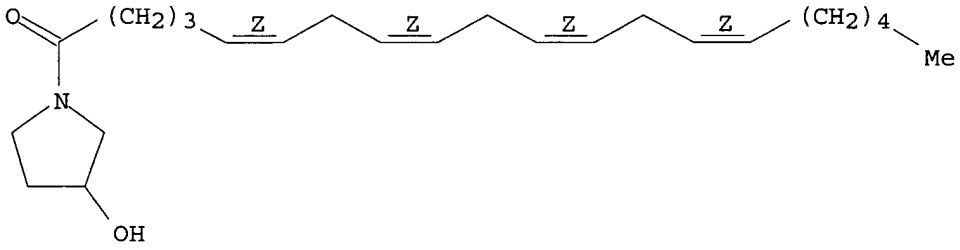


PAGE 1-B



RN 231632-77-2 HCAPLUS
CN 3-Pyrrolidinol, 1-[(5Z,8Z,11Z,14Z)-1-oxo-5,8,11,14-eicosatetraenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 5 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:275785 HCAPLUS
DOCUMENT NUMBER: 131:68487
TITLE: Anandamide-induced mobilization of cytosolic Ca2+ in endothelial cells
AUTHOR(S): Mombouli, Jean-Vivien; Schaeffer, Gabriela; Holzmann, Sigrid; Kostner, Gert M.; Graier, Wolfgang F.
CORPORATE SOURCE: Department of Medical Biochemistry, Karl Franzens University of Graz, Graz, A8010, Austria
SOURCE: British Journal of Pharmacology (**1999**), 126(7), 1593-1600
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Expts. were designed to determine whether anandamide affects cytosolic Ca2+ concns. in endothelial cells and, if so, whether CB1 cannabinoid receptors are involved. To this effect, human umbilical vein-derived EA.hy926 endothelial cells were loaded with fura-2 to monitor changes in cytosolic Ca2+ using conventional fluorescence spectrometry methods. Anandamide induced an increase in Ca2+ in endothelial cells which, in contrast to histamine, developed slowly and was transient. Anandamide caused a concentration-dependent release of Ca2+ from intracellular stores without triggering capacitative Ca2+ entry, contrary to histamine or the endoplasmic reticulum Ca2+-ATPase inhibitor thapsigargin. Anandamide pretreatment slightly reduced the mobilization of Ca2+ from intracellular stores that was evoked by histamine. The mobilization of Ca2+ from intracellular stores evoked by anandamide was impaired by 10 mM caffeine. Anandamide and histamine each significantly increased NO synthase activity in EA.hy926 cells, as determined by the enhanced conversion of L-[3H]-arginine to L-[3H]-citrulline. The CB1 cannabinoid receptor antagonist SR 141716A (1 μM) only produced a marginal reduction of the mobilization of Ca2+ produced by 5 μM anandamide. However, at 5 μM SR 141716A elicited the release of Ca2+ from intracellular stores. This concentration strongly impaired the mobilization of cytosolic Ca2+ evoked by either anandamide, histamine or thapsigargin. Pretreatment of the cells with either 200 μM phenylmethylsulfonyl fluoride (to inhibit the conversion of anandamide into arachidonic acid) or 400 ng/mL pertussis toxin (to uncouple CB1 cannabinoid receptors from Gi/o proteins) had no significant effect on the mobilization of cytosolic Ca2+ evoked by either anandamide, or histamine. Taken together the results demonstrate that anandamide mobilizes Ca2+ from a caffeine-sensitive intracellular Ca2+ store that functionally overlaps in part with the internal stores mobilized by histamine. However, a classical CB1 cannabinoid receptor-mediated and pertussis toxin-sensitive mechanism does not mediate this novel effect of anandamide in endothelial cells. The mobilization of cytosolic Ca2+ in endothelial cells may account for the endothelium-dependent and NO-mediated vasodilator actions of anandamide. Due to its non-specific inhibition of Ca2+ signaling in endothelial cells, SR 141716A may not be used to assess the physiol. involvement of endogenous cannabinoids to endothelium-dependent control of vascular smooth muscle tone.

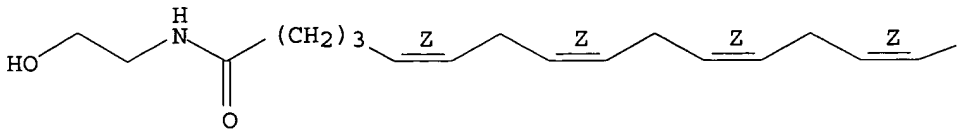
IT **94421-68-8**, **Anandamide**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**anandamide**-induced mobilization of cytosolic calcium in endothelial cells and mechanism therefor)

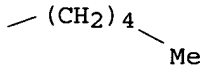
RN 94421-68-8 HCAPLUS

CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A





REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 6 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:226219 HCAPLUS
DOCUMENT NUMBER: 131:1015
TITLE: A role for N-arachidonylethanolamine (anandamide) as the mediator of sensory nerve-dependent Ca2+-induced relaxation
AUTHOR(S): Ishioka, Norio; Bukoski, Richard D.
CORPORATE SOURCE: Section of Hypertension and Vascular Research, University of Texas Medical Branch, Galveston, TX, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (**1999**), 289(1), 245-250
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

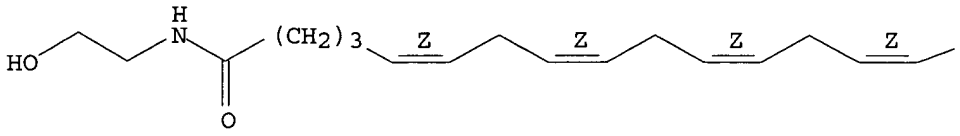
AB We tested the hypothesis that an endogenous cannabinoid (CB) receptor agonist, such as N-arachidonylethanolamine (anandamide), is the transmitter that mediates perivascular sensory nerve-dependent Ca2+-induced relaxation. Rat mesenteric branch arteries were studied using wire myog.; relaxation was determined after inducing contraction with norepinephrine. Cumulative addition of Ca2+ caused dose-dependent relaxation (ED50 = 2.2 mM). The relaxation was inhibited by 10 mM TEA and 100 nM iberiotoxin, a blocker of large conductance Ca2+-activated K+ channels, but not by 5 μM glibenclamide, 1 mM 4-aminopyridine, or 30 nM apamin. Ca2+-induced relaxation was also blocked by the selective CB receptor antagonist SR 141716A and was enhanced by pretreatment with 4-(2-aminoethyl)benzenesulfonyl fluoride hydrochloride (pefabloc; 30 μM), an inhibitor of anandamide metabolism Anandamide also caused dose-dependent relaxation (ED50 = 0.72 μM). The relaxation was not inhibited by endothelial denudation, 10 μM indomethacin, or 1 μM miconazole, but was blocked by 3 μM SR 141716A, 10 mM TEA, precontraction with 100 mM K+, and 100 nM iberiotoxin, and was enhanced by treatment with 30 μM pefabloc. Mesenteric branch arteries were 200-fold more sensitive to the relaxing action of anandamide than arachidonic acid (ED50 = 160 μM). These data show that: (1) Ca2+ and anandamide cause hyperpolarization-mediated relaxation of mesenteric branch arteries, which is dependent on an iberiotoxin-sensitive Ca2+-activated K+ channel, (2) relaxation induced by both Ca2+ and anandamide is inhibited by CB receptor blockade, and (3) relaxation induced by anandamide is not dependent on its breakdown to arachidonic acid and subsequent metabolism These findings support the hypothesis that anandamide, or a similar cannabinoid receptor agonist, mediates nerve-dependent Ca2+-induced relaxation in the rat.

IT **94421-68-8, Anandamide**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**anandamide** mediation of sensory nerve-dependent calcium-induced artery relaxation in rat and mechanism therefor)

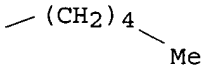
RN 94421-68-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 7 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:811082 HCAPLUS
DOCUMENT NUMBER: 130:218085
TITLE: **Anandamide transport** inhibition by the vanilloid agonist olvanil
AUTHOR(S): Beltramo, Massimiliano; Piomelli, Daniele
CORPORATE SOURCE: The Neurosciences Institute, San Diego, CA, 92121, USA
SOURCE: European Journal of Pharmacology (**1999**), 364(1), 75-78
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

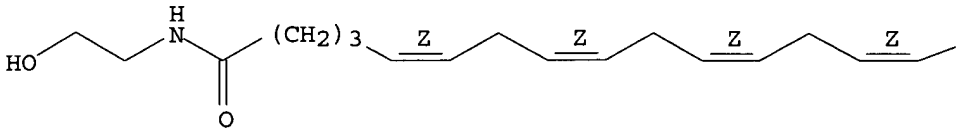
AB The structural similarities between the **anandamide transport** inhibitor N-(4-hydroxyphenyl)-arachidonylamide (AM404) and the synthetic vanilloid agonist olvanil [(N-vanillyl)-9-oleamide], prompted us to investigate the possibility that olvanil may interfere with **anandamide transport.** The intracellular accumulation of [3H]anandamide by human astrocytoma cells was prevented by olvanil with a Ki value of 14.1±7.1 μM. By contrast, capsaicin [(8-methyl-N-vanillyl)-6-noneamide], a plant-derived vanilloid agonist, and capsazepine (N-[2-(4-chlorophenyl)ethyl]-1,3,4,5-tetrahydro-7,8-dihydroxy-2H-2-benzazepine-2-carbothioamide), a vanilloid antagonist, had no such effect (Ki>100 μM). These results indicate that, although less potent than AM404 (Ki 2.1±0.2 μM), olvanil may reduce anandamide clearance at concns. similar to those needed for vanilloid receptor activation.

IT **94421-68-8, Anandamide**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**anandamide transport** inhibition by vanilloid agonist olvanil)

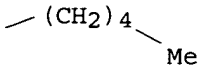
RN 94421-68-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 8 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:625890 HCAPLUS
DOCUMENT NUMBER: 129:326514
TITLE: Evidence against anandamide as the hyperpolarizing factor mediating the nitric oxide-independent coronary vasodilator effect of bradykinin in the rat
AUTHOR(S): Fulton, David; Quilley, John
CORPORATE SOURCE: Department of Pharmacology and Molecular Cardiobiology Division, Boyer Center for Molecular Medicine, Yale University, New Haven, CT, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (**1998**), 286(3), 1146-1151
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The mediator of nitric oxide-(NO) independent vasodilation attributed to endothelium-derived hyperpolarizing factor remains unidentified although there is evidence for a cytochrome P 450-derived eicosanoid. Anandamide, the ethanolamide of arachidonic acid and an endogenous ligand for cannabinoid receptors, was proposed as an endothelium-derived hyperpolarizing factor-mediating mesenteric vasodilation to acetylcholine and the hypotensive effect of bradykinin. Using pharmacol. interventions that attenuate responses to bradykinin, we examined the possibility of anandamide as a mediator of the NO-independent vasodilator effect of bradykinin in the rat perfused heart by determining responses to anandamide and arachidonic acid. Hearts were treated with indomethacin to exclude prostaglandins and nitroarginine to inhibit NO synthesis and elevate perfusion pressure. The cannabinoid receptor antagonist, SR 141716A (2 μM), reduced dose-dependent vasodilator responses to anandamide (1-10 μg) but was without effect on responses to AA (1-10 μg), bradykinin (10-1000 ng) or cromakalim (1-10 μg). Inhibition of voltage-dependent Ca++ channels with nifedipine (5 nM) attenuated vasodilation to anandamide and arachidonic acid whereas inhibition of Ca++-activated K+ channels with charybdotoxin (10 nM) reduced responses to arachidonic acid but had no effect on vasodilation induced by anandamide. Inhibition of cytochrome P 450 with clotrimazole (1 μM) greatly reduced vasodilator responses to bradykinin with less effect on those to anandamide. Finally, the time

course of the coronary vasodilator responses to anandamide and bradykinin were dissimilar. These results argue against a role of anandamide in the vasodilator effect of bradykinin in the rat heart.

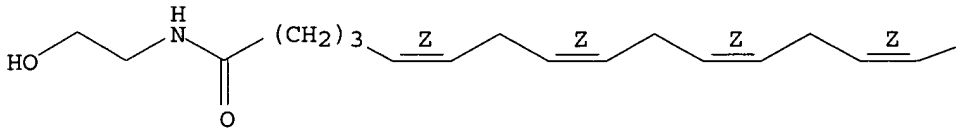
IT **94421-68-8**, **Anandamide**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**anandamide** is not hyperpolarizing factor mediating nitric oxide-independent coronary vasodilator effect of bradykinin in rats)

RN 94421-68-8 HCAPLUS

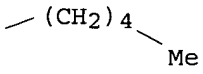
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 9 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1998:61284 HCAPLUS

DOCUMENT NUMBER: 128:213651

TITLE: Dual effects of anandamide on NMDA receptor-mediated responses and neurotransmission

AUTHOR(S): Hampson, Aidan J.; Bornheim, Lester M.; Scanziani, Massimo; Yost, C. Spencer; Gray, Andrew T.; Hansen, Bonnie M.; Leonoudakis, Dmitri J.; Bickler, Philip E.

CORPORATE SOURCE: Departments of Cellular and Molecular Pharmacology, University of California San Francisco, San Francisco, CA, USA

SOURCE: Journal of Neurochemistry (**1998**), 70(2), 671-676
CODEN: JONRA9; ISSN: 0022-3042

PUBLISHER: Lippincott-Raven Publishers

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Anandamide is an endogenous ligand of cannabinoid receptors that induces pharmacol. responses in animals similar to those of cannabinoids such as Δ9-tetrahydrocannabinol (THC). Typical pharmacol. effects of cannabinoids include disruption of pain, memory formation, and motor coordination, systems that all depend on NMDA receptor mediated neurotransmission. The authors investigated whether anandamide can influence NMDA receptor activity by examining NMDA-induced calcium flux (ΔCaNMDA2+) in rat brain slices. The presence of anandamide reduced ΔCaNMDA2+ and the inhibition was disrupted by cannabinoid receptor antagonist, pertussis toxin treatment, and agatoxin (a calcium channel

inhibitor). Whereas these treatments prevented anandamide inhibiting ΔCaNMDA2+, they also revealed another, underlying mechanism by which anandamide influences ΔCaNMDA2+. In the presence of cannabinoid receptor antagonist, anandamide potentiated ΔCaNMDA2+ in cortical, cerebellar, and hippocampal slices. Anandamide (but not THC) also augmented NMDA-stimulated currents in Xenopus oocytes expressing cloned NMDA receptors, suggesting a capacity to directly modulate NMDA receptor activity. In a similar manner, anandamide enhanced neurotransmission across NMDA receptor-dependent synapses in hippocampus in a manner that was not mimicked by THC and was unaffected by cannabinoid receptor antagonist. These data demonstrate that anandamide can modulate NMDA receptor activity in addition to its role as a cannabinoid receptor ligand.

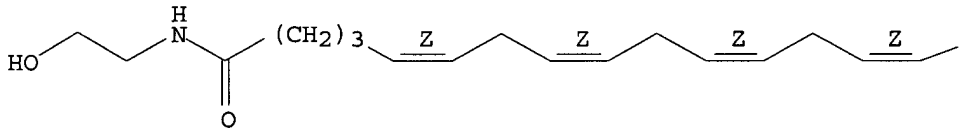
IT **94421-68-8, Anandamide**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**anandamide** dual effects of on NMDA receptor-mediated responses and neurotransmission)

RN 94421-68-8 HCAPLUS

CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



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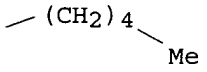


REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 10 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:6093 HCAPLUS
DOCUMENT NUMBER: 128:124053
TITLE: A comparison of EDHF-mediated and anandamide-induced relaxations in the rat isolated mesenteric artery
AUTHOR(S): White, Richard; Hiley, C. Robin
CORPORATE SOURCE: Department of Pharmacology, University of Cambridge, Cambridge, CB2 1QJ, UK
SOURCE: British Journal of Pharmacology (**1997**), 122(8), 1573-1584
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Relaxation of the methoxamine-precontracted rat small mesenteric artery by endothelium-derived hyperpolarizing factor (EDHF) was compared with relaxation to the cannabinoid, anandamide (arachidonylethanolamide). EDHF was produced in a concentration- and endothelium-dependent fashion in the

presence of NG-nitro-L-arginine Me ester (L-NAME, 100 μM) by either carbachol (pEC50 [neg. logarithm of the EC50] = 6.19, Rmax [maximum response] = 93.2%) or calcium ionophore A23187 (pEC50 = 6.46, Rmax = 83.6%). Anandamide responses were independent of the presence of endothelium or L-NAME (control with endothelium: pEC50 = 6.31, Rmax = 94.7%; with L-NAME: pEC50 = 6.33, Rmax = 93.4%). The selective cannabinoid receptor antagonist, SR 141716A (1 μM) caused rightward shifts of the concentration-response curves to both carbachol (2.5-fold) and A23187 (3.3-fold).

It also antagonized anandamide relaxations in the presence or absence of endothelium giving a 2-fold shift in each case. SR 141716A (10 μM) greatly reduced the Rmax values for EDHF-mediated relaxations to carbachol (control, 93.2%; SR 141716A, 10.7%) and A23187 (control, 84.8%; SR 141716A, 3.5%) but caused a 10-fold parallel shift in the concentration-relaxation curve for anandamide without affecting Rmax. Precontraction with 60 mM KCl significantly reduced relaxations to 1 μM carbachol (control 68.8% vs. 17.8%), A23187 (control 71.4% vs. 9%) and anandamide (control 71.1% vs. 2%). Similar effects were seen in the presence of 25 mM K+. Incubation of vessels with pertussis toxin (PTX; 400 ng ml-1, 2 h) also reduced relaxations to 1 μM carbachol (control 63.5% vs. 0%), A23187 (control 77.0% vs. 16.2%) and anandamide (control 89.8% vs. 17.6%). Incubation of vessels with the protease inhibitor phenylmethylsulfonyl fluoride (PMSF; 200 μM) significantly potentiated, to a similar extent (.apprx. 2-fold), relaxation to A23187 (pEC50: control, 6.45; PMSF, 6.74) and anandamide (pEC50: control, 6.31; PMSF, 6.61). PMSF also potentiated carbachol responses both in the presence (pEC50: control, 6.25; PMSF, 7.00) and absence (pEC50: control, 6.41; PMSF, 6.88) of L-NAME. Responses to the nitric oxide donor S-nitroso-N-acetylpenicillamine (SNAP) were also potentiated by PMSF (pEC50: control, 7.51; PMSF, 8.00). EDHF-mediated relaxation to carbachol was significantly attenuated by the K+ channel blocker tetraethylammonium (TEA; 1 mM) (pEC50: control, 6.19; TEA, 5.61). In contrast, TEA (1 mM) had no effect on EDHF-mediated relaxation to A23187 (pEC50: control, 6.47; TEA, 6.41) or on anandamide (pEC50: control, 6.28; TEA, 6.09). TEA (10 mM) significantly reduced the Rmax for anandamide (control, 94.3%; 10 mM TEA, 60.7%) but had no effect on the Rmax to carbachol or A23187. BaCl2 (100 μM), considered to be selective for blockade of inward rectifier K+ channels, had no significant effect on relaxations to carbachol or A23187, but caused a small shift in the anandamide concentration-response curve (pEC50: control, 6.39; Ba2+, 6.20). BaCl2 (1 mM; which causes non-selective block of K+ channels) significantly attenuated relaxations to all three agents (pEC50 values: carbachol, 5.65; A23187, 5.84; anandamide, 5.95). Apamin (1 μM), a selective blocker of small conductance, Ca2+-activated, K+ channels (SKCa), 4-aminopyridine (1 mM), a blocker of delayed rectifier, voltage-dependent, K+ channels (Kv), and ciclazindol (10 μM), an inhibitor of Kv and ATP-sensitive K+ channels (KATP), significantly reduced EDHF-mediated relaxations to carbachol, but had no significant effects on A23187 or anandamide responses. Glibenclamide (10 μM), a KATP inhibitor and charybdotoxin (100 or 300 nM), a blocker of several K+ channel subtypes, had no significant effect on relaxations to any of the agents. Iberiotoxin (50 nM), an inhibitor of large conductance, Ca2+-activated, K+ channels (BKCa), had no significant effect on the relaxation responses, either alone or in combination with apamin (1 μM). Also, a combination of apamin (1 μM) with either glibenclamide (10 μM) or 4-aminopyridine (1 mM) did not inhibit relaxation to carbachol significantly more than apamin alone. Neither combination had any significant effect on relaxation to A23187 or anandamide. A combination of apamin (1 μM) with charybdotoxin (100 nM) abolished EDHF-mediated relaxation to carbachol, but had no significant effect on that to A23187. Apamin (1 μM) and charybdotoxin (300 nM)

together consistently inhibited the response to A23187, while apamin (1 μM) and ciclazindol (10 μM) together inhibited relaxations to both carbachol and A23187. None of these toxin combinations had any significant effect on relaxation to anandamide. It was concluded that the differential sensitivity to K+ channel blockers of EDHF-mediated responses to carbachol and A23187 might be due to actions on endothelial generation of EDHF, as well as its actions on the vascular smooth muscle, and suggests care must be taken in choosing the means of generating EDHF when making comparative studies. Also, the relaxations to EDHF and anandamide may involve activation of cannabinoid receptors, coupled via PTX-sensitive G-proteins to activation of K+ conductances. The results support the hypothesis that EDHF is an endocannabinoid but relaxations to EDHF and anandamide show differential sensitivity to K+ channel blockers, therefore it is likely that anandamide is not identical to EDHF in the small rat mesenteric artery.

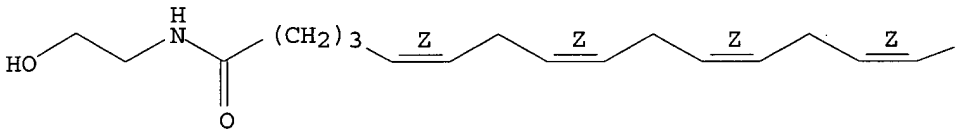
IT **94421-68-8, Anandamide**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(EDHF-mediated and **anandamide**-induced relaxations in isolated mesenteric artery)

RN 94421-68-8 HCAPLUS

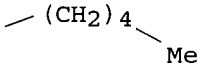
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 11 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1997:808015 HCAPLUS

DOCUMENT NUMBER: 128:136686

TITLE: Inhibition of intestinal motility by anandamide, an endogenous cannabinoid

AUTHOR(S): Calignano, Antonio; La Rana, Giovanna; Makriyannis, Alexandros; Lin, Sun Y.; Beltramo, Massimiliano; Piomelli, Daniele

CORPORATE SOURCE: Department of Experimental Pharmacology, University of Naples, Naples 80123, Italy

SOURCE: European Journal of Pharmacology (**1997**), 340(2/3), R7-R8
CODEN: EJPHAZ; ISSN: 0014-2999

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The endogenous cannabinoid ligand anandamide (arachidonylethanolamide) inhibited the intestinal passage of a charcoal meal when administered s.c. in mice at doses ranging from 0.1 to 50 mg/kg. This effect was prevented by the cannabinoid CB1 receptor antagonist SR141716A [N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide·HCl] (1 mg/kg s.c.), but it was not affected by the **anandamide transport** inhibitor, N-(4-hydroxyphenyl) arachidonylethanolamide (AM404) (50 mg/kg, s.c.). The results indicate that anandamide modulates intestinal motility in mice by activating cannabinoid CB1 receptors. They also suggest that **anandamide transport**, which was previously shown to participate in terminating neural and vascular responses to anandamide, does not contribute to anandamide inactivation in intestinal tissue.

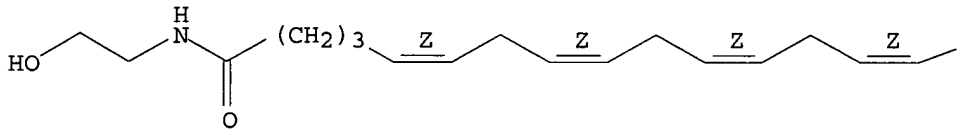
IT **94421-68-8**, **Anandamide**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(intestinal motility inhibition by **anandamide** mediation by cannabinoid receptors)

RN 94421-68-8 HCAPLUS

CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



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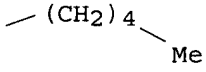


REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 12 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1997:646587 HCAPLUS

DOCUMENT NUMBER: 127:329390

TITLE: Potentiation of **anandamide** hypotension by the **transport** inhibitor, AM404

AUTHOR(S): Calignano, Antonio; La Rana, Giovanna; Beltramo, Massimiliano; Makriyannis, Alexandros; Piomelli, Daniele

CORPORATE SOURCE: Department of Experimental Pharmacology, University of Naples, Naples, 80123, Italy

SOURCE: European Journal of Pharmacology (**1997**), 337(1), R1-R2
CODEN: EJPHAZ; ISSN: 0014-2999

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

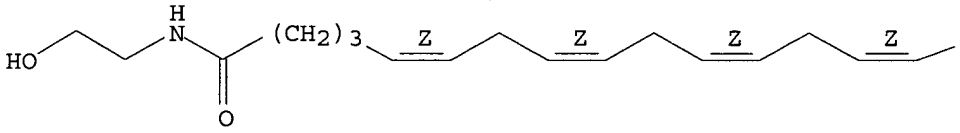
AB The putative endogenous cannabinoid, anandamide (0.2-2 mg/kg i.v.), decreased systemic blood pressure dose-dependently in anesthetized guinea pigs. These effects were prevented by the CB1 cannabinoid receptor antagonist SR141716A [N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide·HCl] at the dose of 0.2 mg/kg i.v. The vasodepressor responses to anandamide were significantly potentiated and prolonged by a novel inhibitor of carrier-mediated **anandamide transport**, N-(4-hydroxyphenyl) arachidonylethanolamide (AM404) (10 mg/kg, i.v.). These results suggest that **anandamide transport** participates in terminating the vascular actions of anandamide.

IT **94421-68-8**, **Anandamide 183718-77-6**, AM 404
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(potentiation of **anandamide** hypotension by **transport** inhibitor, AM404)

RN 94421-68-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



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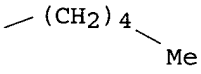
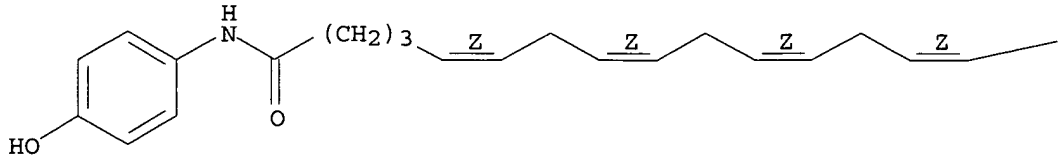


RN 183718-77-6 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-(4-hydroxyphenyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



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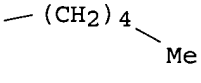


REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

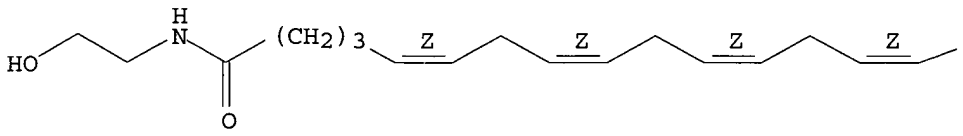
L19 ANSWER 13 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:550217 HCAPLUS
DOCUMENT NUMBER: 127:246072
TITLE: Functional role of high-affinity **anandamide transport**, as revealed by selective inhibition
AUTHOR(S): Beltramo, M.; Stella, N.; Calignano, A.; Lin, S. Y.; Makriyannis, A.; Piomelli, D.
CORPORATE SOURCE: The Neurosciences Inst., San Diego, CA, 92121, USA
SOURCE: Science (Washington, D. C.) (**1997**), 277(5329), 1094-1097
CODEN: SCIEAS; ISSN: 0036-8075
PUBLISHER: American Association for the Advancement of Science
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Anandamide, an endogenous ligand for central cannabinoid receptors, is released from neurons on depolarization and rapidly inactivated. Anandamide inactivation is not completely understood, but it may occur by transport into cells or by enzymic hydrolysis. The compound N-(4-hydroxyphenyl)arachidonylamide (AM404) was shown to inhibit high-affinity anandamide accumulation in rat neurons and astrocytes in vitro, an indication that this accumulation resulted form carrier-mediated transport. Although AM404 did not activate cannabinoid receptors or inhibit anandamide hydrolysis, it enhanced receptor-mediated anandamide responses in vitro and in vivo. The data indicate that carrier-mediated transport may be essential for termination of the biol. effects of anandamide, and may represent a potential drug target.

IT **94421-68-8, Anandamide**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(carrier-mediated **transport** of **anandamide**)
RN 94421-68-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



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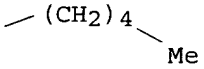


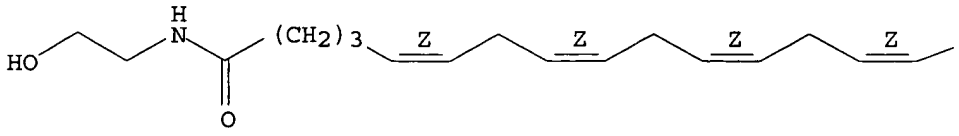
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

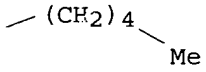
L19 ANSWER 14 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1997:495779 HCAPLUS
DOCUMENT NUMBER: 127:188622
TITLE: Accumulation of N-arachidonoylethanolamine (anandamide) into cerebellar granule cells occurs via facilitated diffusion
AUTHOR(S): Hillard, Cecilia J.; Edgemond, William S.; Jarrahian, Abbas; Campbell, William B.
CORPORATE SOURCE: Department of Pharmacology and Toxicology, Medical College of Wisconsin, Milwaukee, WI, 53226, USA
SOURCE: Journal of Neurochemistry (**1997**), 69(2), 631-638
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Lippincott-Raven
DOCUMENT TYPE: Journal
LANGUAGE: English
AB N-Arachidonoylethanolamine (anandamide, AEA) is a putative endogenous ligand of the cannabinoid receptor. Intact cerebellar granule neurons in primary culture rapidly accumulate AEA. [3H]AEA accumulation by cerebellar granule cells is dependent on incubation time (t1/2 of 2.6 ± 0.8 min at 37°C) and temperature The accumulation of AEA is saturable and has an apparent Km of 41 ± 15 μM and a Vmax of 0.61 ± 0.04 nmol/min/106 cells. [3H]AEA,accumulation by cerebellar granule cells is significantly reduced by 200 μM phloretin (57.4 ± 4% of control) in a noncompetitive manner. [3H]AEA accumulation is not inhibited by either ouabain or removal of extracellular sodium. [3H]AEA accumulation is fairly selective for AEA among other naturally occurring N-acylethanolamines; only N-oleoylethanolamine significantly inhibited [3H]AEA accumulation at a concentration of 10 μM. The ethanolamides of palmitic acid and linolenic acid were inactive at 10 μM. N-Arachidonoylbenzylamine and N-arachidonoylpropylamine, but not arachidonic acid, 15-hydroxy-AEA, or 12-hydroxy-AEA, compete for AEA accumulation. When cells are preloaded with [3H]AEA, temperature-dependent efflux occurs with a half-life of 1.9 ± 1.0 min. Phloretin does not inhibit [3H]AEA efflux from cells. These results suggest that AEA is accumulated by cerebellar granule cells by a protein-mediated transport process that has the characteristics of facilitated diffusion.
IT **94421-68-8, Anandamide**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(accumulation of N-arachidonoylethanolamine into cerebellar granule cells occurs via facilitated diffusion)
RN 94421-68-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A





L19 ANSWER 15 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:457567 HCAPLUS
DOCUMENT NUMBER: 127:145064
TITLE: The biodisposition and metabolism of anandamide in mice
AUTHOR(S): Schwartz, Dean D.
CORPORATE SOURCE: Dep. of Physiology and Pharmacology, College of Veterinary Medicine, Auburn University, AL, 36849, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (**1997**), 282(1), 243-247
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

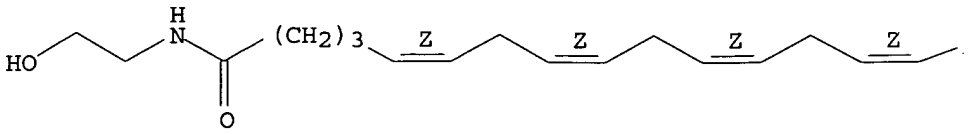
AB The endogenous cannabinoid anandamide (AN) has been reported to produce pharmacol. effects similar to those of Δ9-tetrahydrocannabinol but with a shorter duration of action. Also AN is known to be metabolized to arachidonic acid. The purpose of this study was to examine the time course of distribution and metabolism of AN. Male mice were each administered 20 μCi 3H-AN and 50 mg/kg AN i.v. At 1, 5, 15, and 30 min after administration, the animals were sacrificed, and various tissues were removed, solubilized, and counted to determine the distribution of 3H. Also, samples from brain, adrenal gland, and plasma were extracted with Et acetate and analyzed by HPLC to sep. 3H-labeled AN, arachidonic acid, and other metabolites. AN was detectable in brain by 1 min after injection. At 1 min after injection, the rank order of radioactivity per mg or microliter of tissue was adrenal > lung > kidney > plasma > heart > liver > diaphragm > brain > fat. Although the 1 and 5 min metabolic profiles of brain 3H showed that AN was clearly present, most AN had already been transformed to arachidonic acid and other polar metabolites, and there were almost no detectable brain levels of AN at 15 and 30 min. In plasma and adrenal gland, AN was the predominant forma at 1 and 5 min. Our expts. confirm that AN quickly reaches the brain and suggest that rapid metabolism of AN plays a key role in the time course of the pharmacol. activity of this naturally occurring cannabinoid receptor ligand.

IT **94421-68-8, Anandamide**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(biodisposition and metabolism of **anandamide** in mice)

RN 94421-68-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



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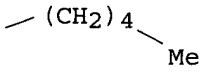
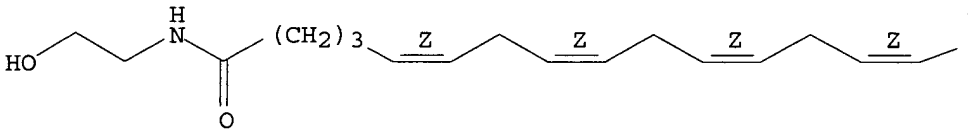


IT **94421-68-8D**, **Anandamide**, metabolites
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(biodisposition and metabolism of **anandamide** in mice)
RN 94421-68-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



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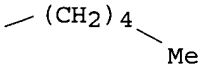


L19 ANSWER 16 OF 16 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:272465 HCAPLUS
DOCUMENT NUMBER: 122:52236
TITLE: Formation and inactivation of endogenous cannabinoid anandamide in central neurons
AUTHOR(S): Di Marzo, Vicenzo; Fontana, Angelo; Cadas, Hugues; Schinelli, Sergio; Cimino, Guido; Schwartz, Jean-Charles; Piomelli, Daniele
CORPORATE SOURCE: Unite de Neurobiologie et Pharmacologie, Centre Paul Broca de I'INSERM, Paris, Fr.
SOURCE: Nature (London) (**1994**), 372(6507), 686-91
CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER: Macmillan Magazines
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Anandamide (N-arachidonoyl-ethanolamine) was recently identified as a

brain arachidonate derivative that binds to and activates cannabinoid receptors, yet the mechanisms underlying formation, release and inactivation of this putative messenger mol. are still unclear. Here the authors report that anandamide is produced in and released from cultured brain neurons in a calcium ion-dependent manner when the neurons are stimulated with membrane-depolarizing agents. Anandamide formation occurs through phosphodiesterase-mediated cleavage of a novel phospholipid precursor, N-arachidonoyl-phosphatidylethanolamine. A similar mechanism also governs the formation of a family of anandamide congeners, whose possible roles in neuronal signaling remain unknown. Therefore, multiple biochem. pathways may participate in anandamide formation in brain tissue. The life span of extracellular anandamide is limited by a rapid and selective process of cellular uptake, which is accompanied by hydrolytic degradation to ethanolamine and arachidonate. The results thus strongly support the proposed role of amandamide as an endogenous neuronal messenger.

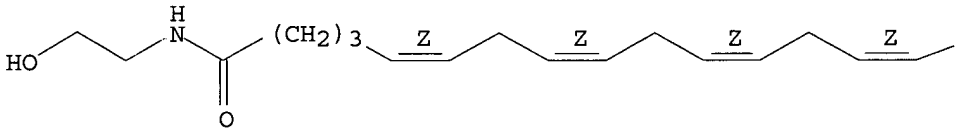
IT **94421-68-8, Anandamide**
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(endogenous cannabinoid **anandamide** formation and inactivation in central neurons)

RN 94421-68-8 HCAPLUS

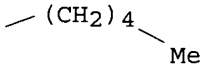
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



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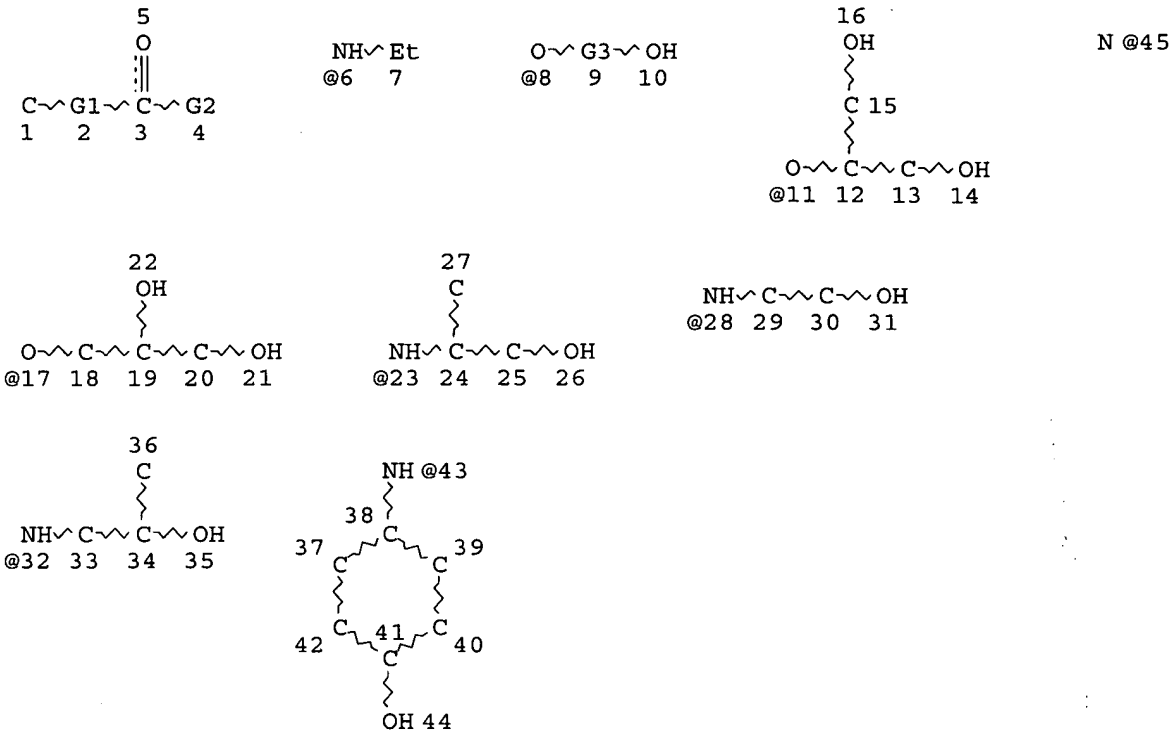

Page 1-A

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Page 1-B
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REP G3=(4-4) C
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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS 45

STEREO ATTRIBUTES: NONE
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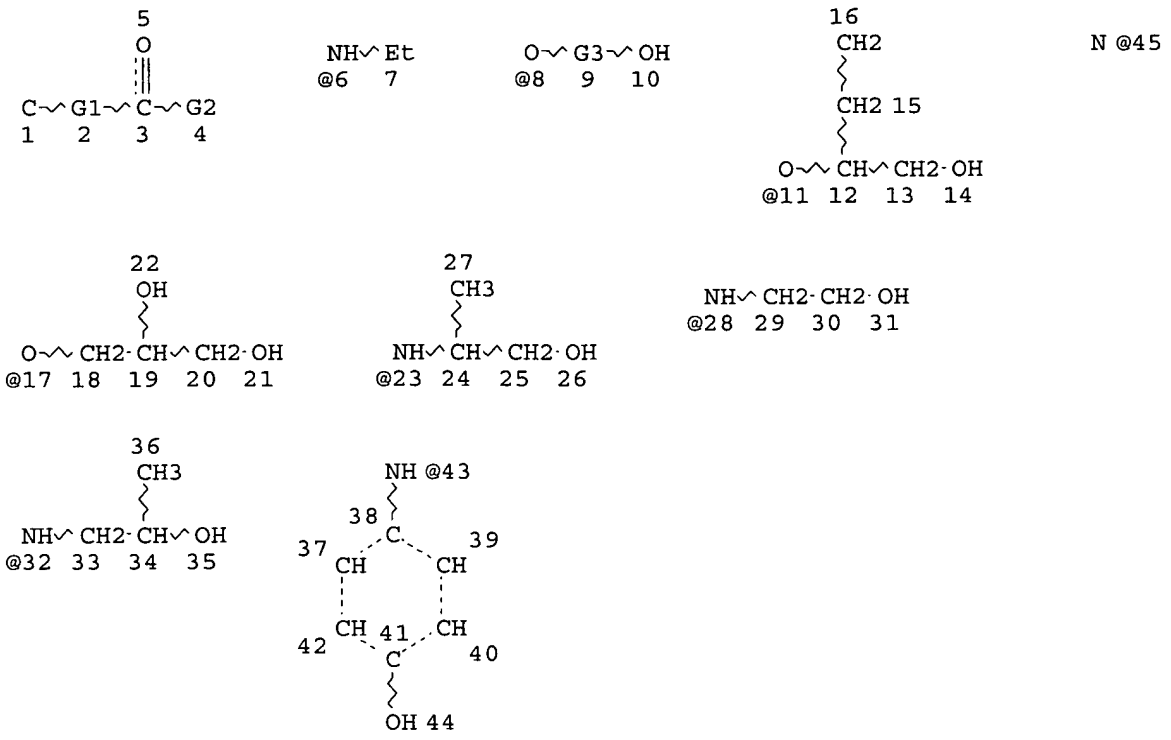
L3 STR



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REP G3=(4-4) C
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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 45

STEREO ATTRIBUTES: NONE

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L6	6	SEA FILE=REGISTRY ABB=ON PLU=ON ANANDAMIDE/BI	
L7	9449	SEA FILE=HCAPLUS ABB=ON PLU=ON L5	
L8	1727	SEA FILE=HCAPLUS ABB=ON PLU=ON L6 OR ?ANANDAMIDE?	
L10	1212	SEA FILE=HCAPLUS ABB=ON PLU=ON L7(L)L8	
L11	684210	SEA FILE=HCAPLUS ABB=ON PLU=ON TRANSPORT/CV OR TRANSPORT	
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L18	120	SEA FILE=HCAPLUS ABB=ON PLU=ON L10 AND L17	
L19	16	SEA FILE=HCAPLUS ABB=ON PLU=ON L18 AND PD=<SEPTEMBER 20, 1999	
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L27 ANSWER 1 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:662262 HCAPLUS
DOCUMENT NUMBER: 132:18705
TITLE: Cannabinoids enhance NMDA-elicited Ca2+ signals in cerebellar granule neurons in culture
AUTHOR(S): Netzeband, Jeffrey G.; Conroy, Shannon M.; Parsons, Kathy L.; Gruol, Donna L.
CORPORATE SOURCE: Department of Neuropharmacology, The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Journal of Neuroscience (**1999**), 19(20), 8765-8777
CODEN: JNRSDS; ISSN: 0270-6474
PUBLISHER: Society for Neuroscience
DOCUMENT TYPE: Journal
LANGUAGE: English

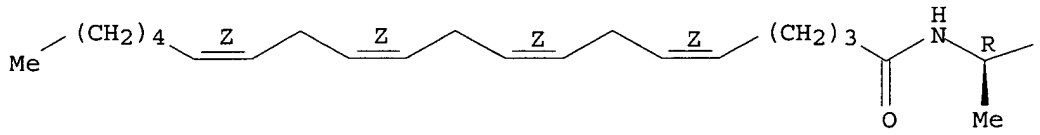
AB A physiol. role for cannabinoids in the CNS is indicated by the presence of endogenous cannabinoids and cannabinoid receptors. However, the cellular mechanisms of cannabinoid actions in the CNS have yet to be fully defined. In the current study, we identified a novel action of cannabinoids to enhance intracellular Ca2+ responses in CNS neurons. Acute application of the cannabinoid receptor agonists R(+)-**methanandamide**, R(+)-WIN, and HU-210 (1-50 nM) dose-dependently enhanced the peak amplitude of the Ca2+ response elicited by stimulation of the NMDA subtype of glutamate receptors (NMDARs) in cerebellar granule neurons. The cannabinoid effect was blocked by the cannabinoid receptor antagonist SR141716A and the Gi/Go protein inhibitor pertussis toxin but was not mimicked by the inactive cannabinoid analog S(-)-WIN, indicating the involvement of cannabinoid receptors. In current-clamp studies neither R(+)-WIN nor R(+)-**methanandamide** altered the membrane response to NMDA or passive membrane properties of granule neurons, suggesting that NMDARs are not the primary sites of cannabinoid action. Addnl. Ca2+ imaging studies showed that cannabinoid enhancement of the Ca2+ signal to NMDA did not involve N-, P-, or L-type Ca2+ channels but was dependent on Ca2+ release from intracellular stores. Moreover, the phospholipase C inhibitor U-73122 and the inositol 1,4,5-trisphosphate (IP3) receptor antagonist xestospongin C blocked the cannabinoid effect, suggesting that the cannabinoid enhancement of NMDA-evoked Ca2+ signals results from enhanced release from IP3-sensitive Ca2+ stores. These data suggest that the CNS cannabinoid system could serve a critical modulatory role in CNS neurons through the regulation of intracellular Ca2+ signaling.

IT **157182-49-5**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(cannabinoids enhance NMDA-elicited Ca2+ signals in cerebellar granule neurons in culture)

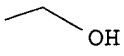
RN 157182-49-5 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-[(1R)-2-hydroxy-1-methylethyl]-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:477906 HCAPLUS
DOCUMENT NUMBER: 131:237872
TITLE: Internalization and recycling of the CB1 cannabinoid receptor
AUTHOR(S): Hsieh, C.; Brown, S.; Derleth, C.; Mackie, K.
CORPORATE SOURCE: Departments of Physiology and Biophysics and of Anesthesiology, University of Washington School of Medicine, Seattle, WA, USA
SOURCE: Journal of Neurochemistry (**1999**), 73(2), 493-501
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

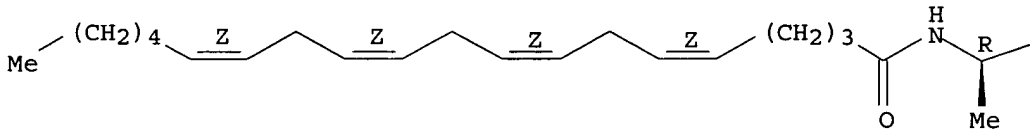
AB Tolerance develops rapidly to cannabis, cannabinoids, and related drugs acting at the CB1 cannabinoid receptor. However, little is known about what happens to the receptor as tolerance is developing. In this study, we have found that CB1 receptors are rapidly internalized following agonist binding and receptor activation. Efficacious cannabinoid agonists (WIN 55,212-2, CP 55,940, and HU 210) caused rapid internalization. **Methanandamide** (an analog of an endogenous cannabinoid, **anandamide**) was less effective, causing internalization only at high concentration, whereas Δ9-tetrahydrocannabinol caused little internalization, even at 3 μM. CB1 internalized via clathrin-coated pits as sequestration was inhibited by hypertonic sucrose. Internalization did not require activated G protein αi, αo, or αs subunits. A region of the extreme carboxy terminus of the receptor was necessary for internalization, as a mutant CB1 receptor lacking the last 14 residues did not internalize, whereas a mutant lacking the last 10 residues did. Steps involved in the recycling of sequestered receptor were also investigated. Recovery of CB1 to the cell surface after short (20 min) but not long (90 min) agonist treatment was independent of new protein synthesis. Recycling also required endosomal acidification and dephosphorylation. These results show that CB1 receptor trafficking is dynamically regulated by cannabimimetic drugs.

IT **157182-49-5**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(internalization and recycling of the CB1 cannabinoid receptor)
RN 157182-49-5 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-[(1R)-2-hydroxy-1-methylethyl]-,

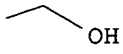
(5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 3 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:441497 HCAPLUS
DOCUMENT NUMBER: 131:179634
TITLE: Cannabinoid CB1 receptor of cat cerebral arterial muscle functions to inhibit L-type Ca2+ channel current
AUTHOR(S): Gebremedhin, Debebe; Lange, Andrew R.; Campbell, William B.; Hillard, Cecilia J.; Harder, David R.
CORPORATE SOURCE: Departments Physiology and Pharmacology and Toxicology and Cardiovascular Res. Center, Medical College Wisconsin, Milwaukee, WI, 53226, USA
SOURCE: American Journal of Physiology (**1999**), 276(6, Pt. 2), H2085-H2093
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The CB1 subtype of the cannabinoid receptor is present on neurons in the brain and mediates the perceptual effects of Δ9-tetrahydrocannabinol and other cannabinoids. The authors found that cat cerebral arterial smooth muscle cells (VSMC) contain the protein for the CB1 receptor and express a cDNA that has >98% amino acid homol. to the CB1 cDNA expressed in rat and human neurons. Activation of the CB1 cannabinoid receptor has been shown to decrease the opening of N-type voltage-gated Ca2+ channels in neurons through a pertussis toxin-sensitive GTP-binding protein. In the present study the authors tested the hypothesis that activation of the cannabinoid CB1 receptor in cerebral VSMC inhibits voltage-gated Ca2+ channels and results in cerebral vasodilation. The predominant Ca2+ current identified in cat cerebral VSMC is a voltage-gated, dihydropyridine-sensitive, L-type Ca2+ current. The cannabimimetic drug WIN-55,212-2 (10-100 nM) induced concentration-dependent inhibition of peak L-type Ca2+ current, which reached a maximum of 82±4% at 100 nM (n = 14). This effect was mimicked by the putative endogenous CB1-receptor agonist **anandamide**, which produced a concentration-related reduction of peak L-type Ca2+ current with a maximum inhibition (at 300 nM) of 39±4% (n = 12). The inhibitory effects of both ligands on peak L-type Ca2+ currents were abolished by pertussis toxin pretreatment and application of the

CB1-receptor antagonist SR-141716A (100 nM, n = 5). Both WIN-55,212-2 and **anandamide** produced concentration-dependent relaxation of preconstricted cerebral arterial segments that was abolished by SR-141716A. These results indicate that the CB1 receptor is expressed in cat cerebral VSMC and that the cerebral vasculature is one of the targets for endogenous cannabinoids. These findings suggest that the CB1 receptor and its endogenous ligand may play a fundamental role in the regulation off cerebral arterial tone and reactivity by modulating the influx of Ca2+ through L-type Ca2+ channels.

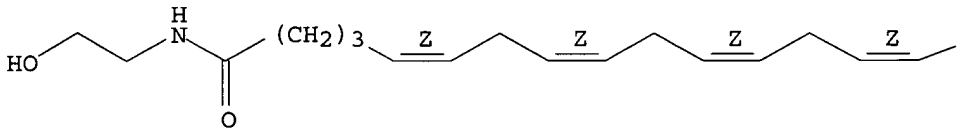
IT **94421-68-8, Anandamide**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(cannabinoid CB1 receptor of cat cerebral arterial muscle functions to inhibit L-type Ca2+ channel current)

RN 94421-68-8 HCAPLUS

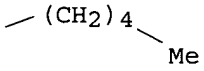
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 4 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:354406 HCAPLUS
DOCUMENT NUMBER: 131:14486
TITLE: Oleamide agonists for inhibition of gap junction communication
INVENTOR(S): Boger, Dale L.; Gilula, Norton B.; Lerner, Richard A.; Cravatt, Benjamin F.
PATENT ASSIGNEE(S): The Scripps Research Institute, USA
SOURCE: PCT Int. Appl., 106 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9926584	A2	19990603	WO 1998-US24913	19981124 <--
WO 9926584	A3	19990715		

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KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,
UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
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JP 2001523695	T2	20011127	JP 2000-521789		19981124
US 6251931	B1	20010626	US 2000-529909		20000419
PRIORITY APPLN. INFO.:			US 1997-977493	A	19971124
			WO 1998-US24913	W	19981124

OTHER SOURCE(S): MARPAT 131:14486

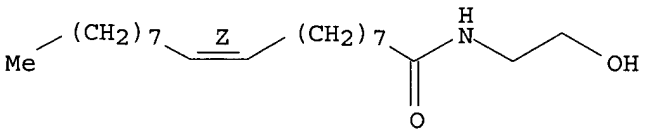
AB Oleamide is an endogenous fatty acid primary amide that possesses sleep-inducing properties in animals and has been shown to effect serotonergic systems and block gap junction communication in a structurally specific manner. Certain agents can serve both as an oleamide agonist and as an inhibitor of fatty acid amide hydrolase. Fatty acid amide hydrolase is responsible for the rapid inactivation of oleamide in vivo. The structural features of oleamide required for inhibition of gap junction-mediated chemical and elec. transmission in rat glial cells are defined. Effective inhibitors fall into two classes of fatty acid primary amides of which oleamide and arachidonamide are the prototypical members. Of these two, oleamide constitutes the most effective and its structural requirements for inhibition of the gap junction are well defined. It requires a chain length of 16-24 carbons of which 16-18 carbons appears optimal, a polarized terminal carbonyl group capable of accepting but not necessarily donating a hydrogen bond, a Δ9 cis double bond, and a hydrophobic Me terminus. Within these constraints, a range of modifications are possible, many of which may be with enhanced in vivo properties.

IT **111-58-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PNU (Preparation, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation)
(oleamide agonists for inhibition of gap junction communication in glial cells)

RN 111-58-0 HCAPLUS

CN 9-Octadecenamide, N-(2-hydroxyethyl)-, (9Z)- (9CI) (CA INDEX NAME)

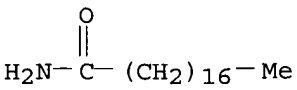
Double bond geometry as shown.



IT **124-26-5**, Stearamide **301-02-0**, Oleamide **94421-68-8 177987-17-6 177987-18-7 177987-27-8**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(oleamide agonists for inhibition of gap junction communication in glial cells)

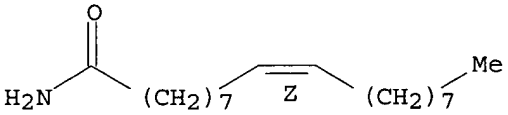
RN 124-26-5 HCAPLUS

CN Octadecanamide (9CI) (CA INDEX NAME)



RN 301-02-0 HCAPLUS
CN 9-Octadecenamide, (9Z)- (9CI) (CA INDEX NAME)

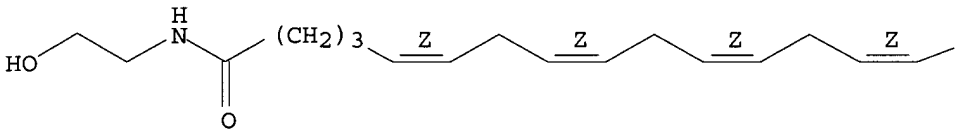
Double bond geometry as shown.



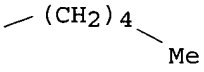
RN 94421-68-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A

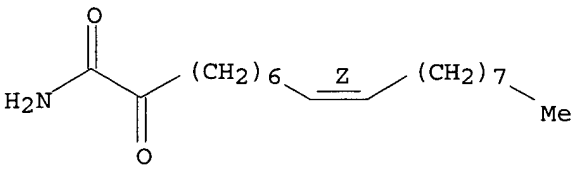


PAGE 1-B



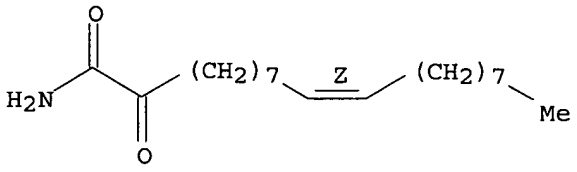
RN 177987-17-6 HCAPLUS
CN 9-Octadecenamide, 2-oxo-, (9Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



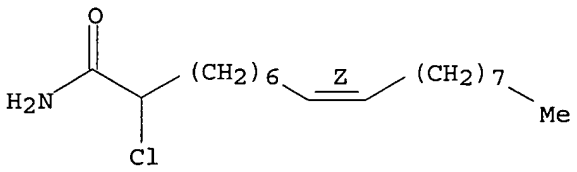
RN 177987-18-7 HCAPLUS
CN 10-Nonadecenamide, 2-oxo-, (10Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



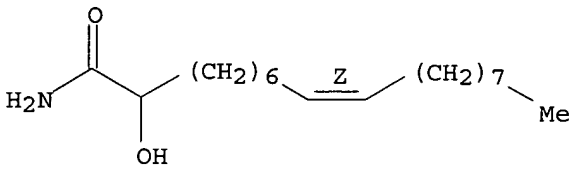
RN 177987-27-8 HCAPLUS
CN 9-Octadecenamide, 2-chloro-, (9Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



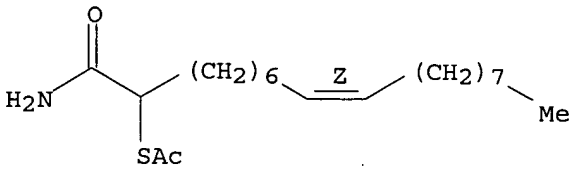
IT **177987-26-7P 208452-48-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(oleamide agonists for inhibition of gap junction communication in glial cells)
RN 177987-26-7 HCAPLUS
CN 9-Octadecenamide, 2-hydroxy-, (9Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 208452-48-6 HCAPLUS
CN Ethanethioic acid, S-[(8Z)-1-(aminocarbonyl)-8-heptadecenyl] ester (9CI) (CA INDEX NAME)

Double bond geometry as shown.

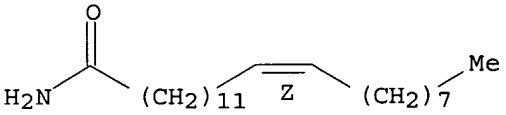


IT **112-84-5P**, Erucamide **3999-01-7P**, Linoleamide **4303-70-2P**, Elaidamide **4637-54-1P 10436-08-5P 24222-02-4P 45281-44-5P 79356-91-5P 85075-82-7P 85146-53-8P**, Arachidonamide

94889-99-3P 117654-34-9P 144194-42-3P,
γ-Linolenamide **164295-11-8P 167782-47-0P,**
Docosahexaenamide **167782-48-1P**, Eicosapentaenamide
172995-11-8P 207512-05-8P 208452-14-6P
208452-17-9P 208452-19-1P 208452-21-5P,
9-Octadecynamide **208452-38-4P 208452-40-8P**
208452-46-4P 208650-27-5P 208650-28-6P
208650-29-7P 208650-30-0P 208650-31-1P
208650-32-2P 208650-33-3P 208650-34-4P
208650-35-5P 208650-36-6P 208650-37-7P,
Nervonamide **208650-39-9P 225943-42-0P**
225943-43-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(oleamide agonists for inhibition of gap junction communication in glial cells)

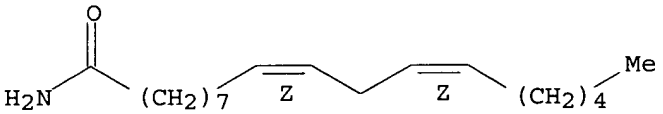
RN 112-84-5 HCAPLUS
CN 13-Docosenamide, (13Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



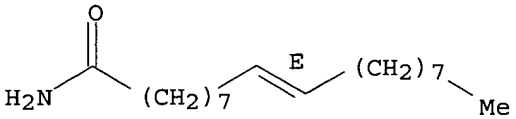
RN 3999-01-7 HCAPLUS
CN 9,12-Octadecadienamide, (9Z,12Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



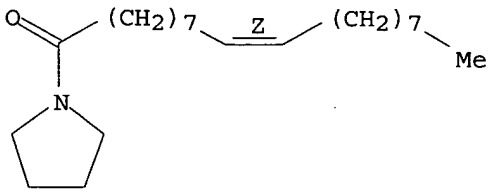
RN 4303-70-2 HCAPLUS
CN 9-Octadecenamide, (9E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



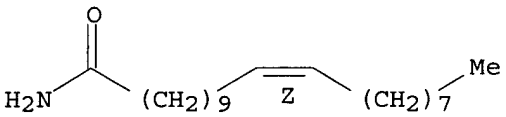
RN 4637-54-1 HCAPLUS
CN Pyrrolidine, 1-[(9Z)-1-oxo-9-octadecenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



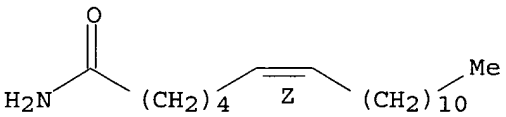
RN 10436-08-5 HCAPLUS
CN 11-Eicosenamide, (11Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



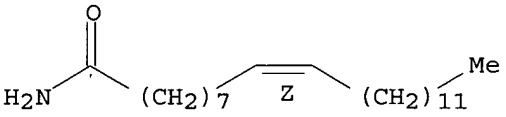
RN 24222-02-4 HCAPLUS
CN 6-Octadecenamide, (6Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



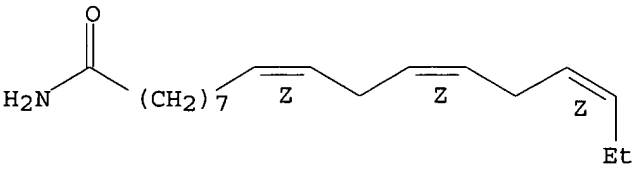
RN 45281-44-5 HCAPLUS
CN 9-Docosenamide, (9Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



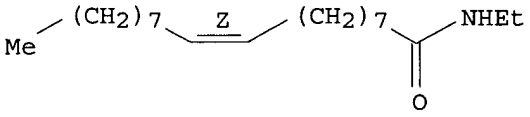
RN 79356-91-5 HCAPLUS
CN 9,12,15-Octadecatrienamide, (9Z,12Z,15Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



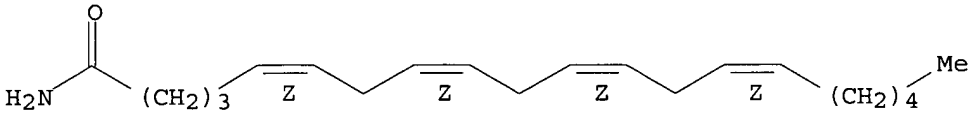
RN 85075-82-7 HCAPLUS
CN 9-Octadecenamide, N-ethyl-, (9Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



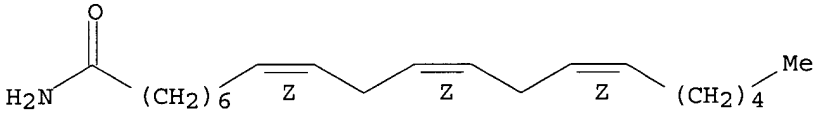
RN 85146-53-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



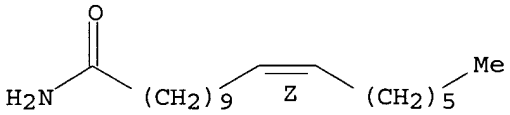
RN 94889-99-3 HCAPLUS
CN 8,11,14-Eicosatrienamide, (8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



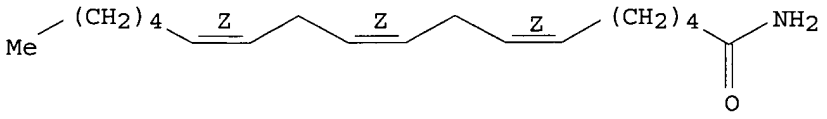
RN 117654-34-9 HCAPLUS
CN 11-Octadecenamide, (11Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



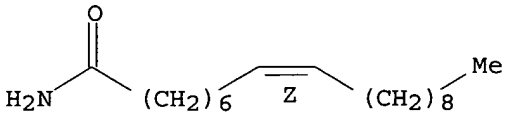
RN 144194-42-3 HCAPLUS
CN 6,9,12-Octadecatrienamide, (6Z,9Z,12Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 164295-11-8 HCAPLUS
CN 8-Octadecenamide, (8Z)- (9CI) (CA INDEX NAME)

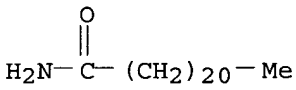
Double bond geometry as shown.



RN 167782-47-0 HCAPLUS
CN Docosahexaenamide (9CI) (CA INDEX NAME)

CM 1

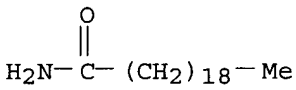
CRN 3061-75-4
CMF C22 H45 N O



RN 167782-48-1 HCAPLUS
CN Eicosapentaenamide (9CI) (CA INDEX NAME)

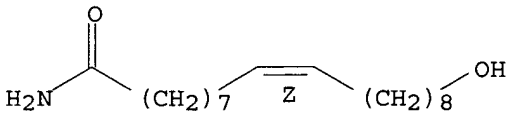
CM 1

CRN 51360-63-5
CMF C20 H41 N O



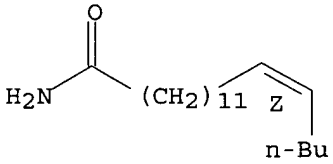
RN 172995-11-8 HCAPLUS
CN 9-Octadecenamide, 18-hydroxy-, (9Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 207512-05-8 HCAPLUS
CN 13-Octadecenamide, (13Z)- (9CI) (CA INDEX NAME)

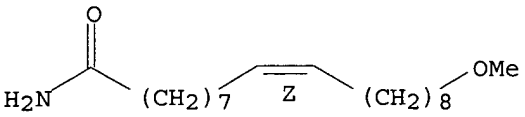
Double bond geometry as shown.



RN 208452-14-6 HCAPLUS

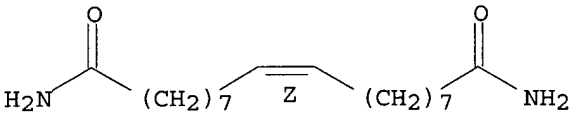
CN 9-Octadecenamide, 18-methoxy-, (9Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



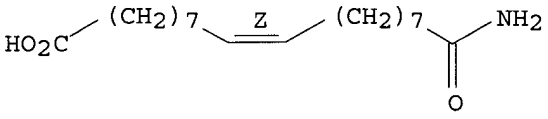
RN 208452-17-9 HCAPLUS
CN 9-Octadecenediamide, (9Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

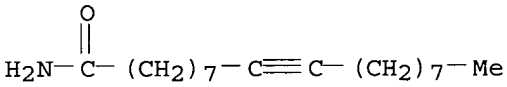


RN 208452-19-1 HCAPLUS
CN 9-Octadecenoic acid, 18-amino-18-oxo-, (9Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

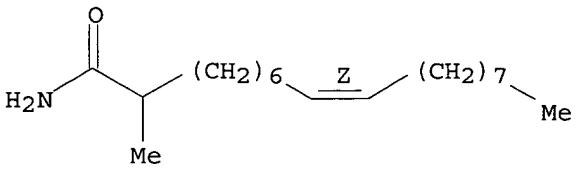


RN 208452-21-5 HCAPLUS
CN 9-Octadecynamide (9CI) (CA INDEX NAME)



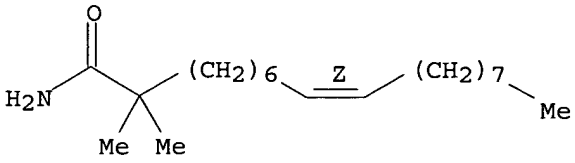
RN 208452-38-4 HCAPLUS
CN 9-Octadecenamide, 2-methyl-, (9Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



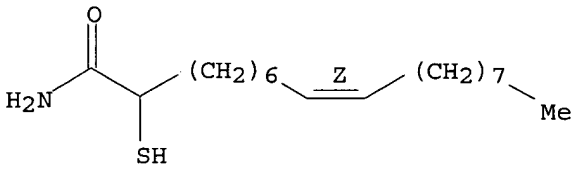
RN 208452-40-8 HCAPLUS
CN 9-Octadecenamide, 2,2-dimethyl-, (9Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



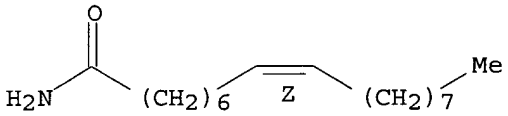
RN 208452-46-4 HCAPLUS
CN 9-Octadecenamide, 2-mercapto-, (9Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



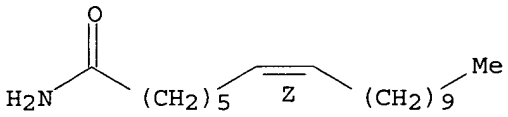
RN 208650-27-5 HCAPLUS
CN 8-Heptadecenamide, (8Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



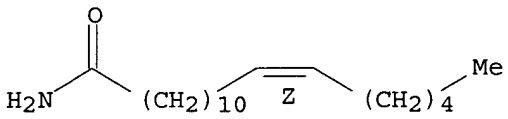
RN 208650-28-6 HCAPLUS
CN 7-Octadecenamide, (7Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



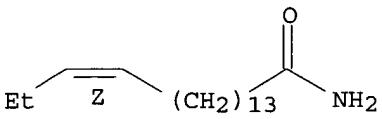
RN 208650-29-7 HCAPLUS
CN 12-Octadecenamide, (12Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



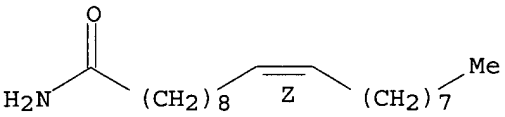
RN 208650-30-0 HCAPLUS
CN 15-Octadecenamide, (15Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



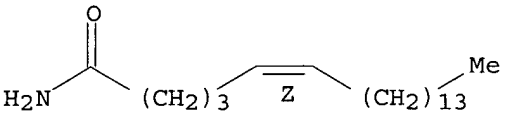
RN 208650-31-1 HCAPLUS
CN 10-Nonadecenamide, (10Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



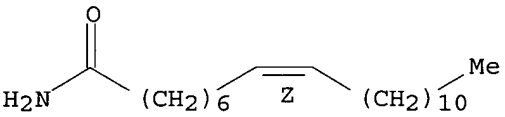
RN 208650-32-2 HCAPLUS
CN 5-Eicosenamide, (5Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



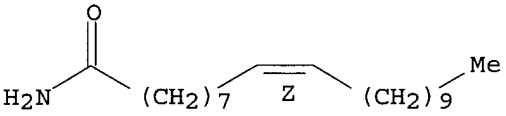
RN 208650-33-3 HCAPLUS
CN 8-Eicosenamide, (8Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



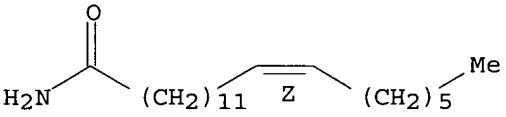
RN 208650-34-4 HCAPLUS
CN 9-Eicosenamide, (9Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



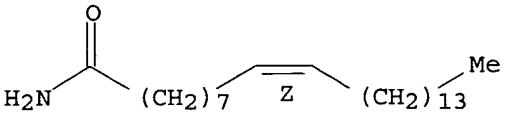
RN 208650-35-5 HCAPLUS
CN 13-Eicosenamide, (13Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



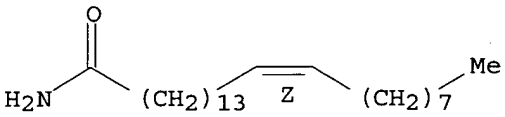
RN 208650-36-6 HCAPLUS
CN 9-Tetracosenamide, (9Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



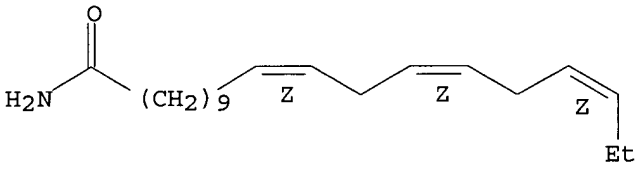
RN 208650-37-7 HCAPLUS
CN 15-Tetracosenamide, (15Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



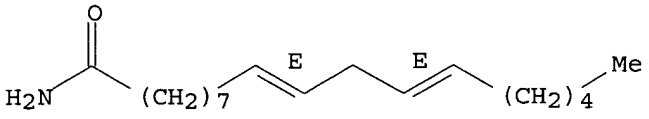
RN 208650-39-9 HCAPLUS
CN 11,14,17-Eicosatrienamide, (11Z,14Z,17Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



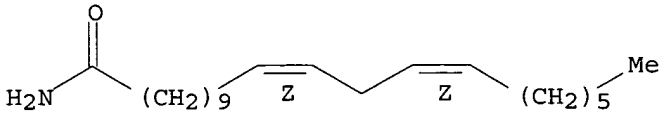
RN 225943-42-0 HCAPLUS
CN 9,12-Octadecadienamide, (9E,12E)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 225943-43-1 HCAPLUS
CN 11,14-Heneicosadienamide, (11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



L27 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN

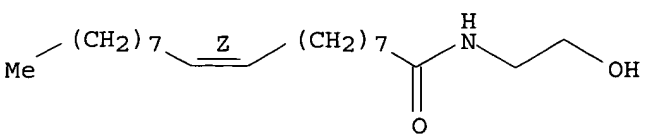
ACCESSION NUMBER: 1998:698015 HCAPLUS
DOCUMENT NUMBER: 130:76092
TITLE: Interactions between synthetic vanilloids and the endogenous cannabinoid system
AUTHOR(S): Di Marzo, Vincenzo; Bisogno, Tiziana; Melck, Dominique; Ross, Ruth; Brockie, Heather; Stevenson, Lesley; Pertwee, Roger; De Petrocellis, Luciano
CORPORATE SOURCE: Istituto per la Chimica di Molecole di Interesse Biologico, CNR, Arco Felice, 80072, Italy
SOURCE: FEBS Letters (**1998**), 436(3), 449-454
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The chemical similarity between some synthetic agonists of vanilloid receptors, such as olvanil (N-vanillyl-cis-9-octadecenoamide), and the 'endocannabinoid' **anandamide** (arachidonoyl-ethanolamide, AEA), suggests possible interactions between the cannabinoid and vanilloid signalling systems. Here the authors report that olvanil is a stable and potent inhibitor of AEA facilitated **transport** into rat basophilic leukemia (RBL-2H3) cells. Olvanil blocked both the uptake and the hydrolysis of [14C]AEA by intact RBL-2H3 cells (IC50 = 9 μM), while capsaicin and pseudocapsaicin (N-vanillyl-nonanamide) were much less active. Olvanil was more potent than previously reported inhibitors of AEA facilitated **transport**, i.e. phloretin (IC50 = 80 μM), AM404 (12.9%, inhibition at 10 μM) or oleoylethanolamide (27.5% inhibition at 10 μM). Olvanil was a poor inhibitor of [14C]AEA hydrolysis by RBL-2H3 and N18TG2 cell membranes, suggesting that the inhibitory effect on [14C]AEA breakdown observed in intact cells was due to inhibition of [14C]AEA uptake. Olvanil was stable to enzymic hydrolysis, and (i) displaced the binding of high affinity cannabinoid receptor ligands to membrane prepns. from N18TG2 cells and guinea pig forebrain (Ki = 1.64-7.08 μM), but not from cells expressing the CB2 cannabinoid receptor subtype; (ii) inhibited forskolin-induced cAMP formation in intact N18TG2 cells (IC50 = 1.60 μM), this effect being reversed by the selective CB1 antagonist SR141716A. Pseudocapsaicin, but not capsaicin, also selectively bound to CB1 receptor-containing membranes. These data suggest that some of the analgesic actions of olvanil may be due to its interactions with the endogenous cannabinoid system, and may lead to the design of a novel class of cannabimimetics with potential therapeutic applications as analgesics.

IT **111-58-0 94421-68-8, Anandamide**
183718-77-6, AM 404
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(interactions between synthetic vanilloids and the endogenous cannabinoid system)

RN 111-58-0 HCAPLUS
CN 9-Octadecenamide, N-(2-hydroxyethyl)-, (9Z)- (9CI) (CA INDEX NAME)

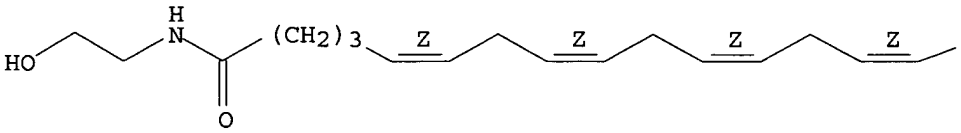
Double bond geometry as shown.



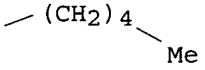
RN 94421-68-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



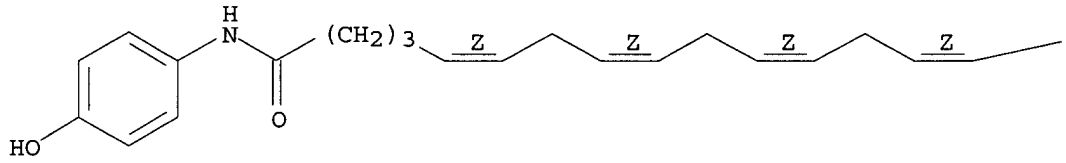
PAGE 1-B



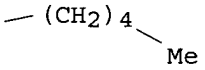
RN 183718-77-6 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-(4-hydroxyphenyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 6 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:694174 HCAPLUS
DOCUMENT NUMBER: 130:75718
TITLE: Exploration of Biologically Relevant Conformations of **Anandamide**, 2-Arachidonylglycerol, and Their Analogs Using Conformational Memories
AUTHOR(S): Barnett-Norris, Judy; Guarnieri, Frank; Hurst, Dow P.; Reggio, Patricia H.
CORPORATE SOURCE: Department of Chemistry, Kennesaw State University, Kennesaw, GA, 30144, USA
SOURCE: Journal of Medicinal Chemistry (**1998**), 41(24), 4861-4872

CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The endogenous cannabinoid **anandamide** (N-arachidonoylethanolamide) has been shown to possess higher affinity for the cannabinoid CB1 receptor than for the CB2 receptor. Carrier-mediated **transport** has been proposed to be essential for the termination of the biol. effects of **anandamide**, while hydrolysis of **anandamide** is performed by a membrane-bound amidohydrolase, fatty acid amidohydrolase (FAAH). As interaction of **anandamide** with each of these targets occurs in different environments, the conformations of **anandamide** for interaction with each target may differ. To ascertain what conformations of **anandamide**, a highly flexible mol., are favored in polar and nonpolar environments, the new method of Conformational Memories (CM) was used. CM has been shown to achieve complete conformational sampling of highly flexible ligands, to converge in a very practical number of steps, and to be capable of overcoming energy barriers very efficiently (Guarnieri et al. J. Am. Chemical Society 1996, 118, 5580). The generalized Born/surface area (GB/SA) continuum solvation models for chloroform and for water were used in the CM calcns. As a means of validation, CM was first applied to arachidonic acid because both exptl. and theor. conformational studies of arachidonic acid have been reported. CM was also applied to sn-2-arachidonylglycerol (2-AG), another endogenous CB ligand; to a 1,1-dimethylheptyl derivative of **anandamide** , an analog with higher CB1 affinity than **anandamide**; and to N-(2-hydroxyethyl)prostaglandin-B2-ethanolamide (PGB2-EA), a prostanoid ligand which does not bind to CB1. Consistent with the literature, arachidonic acid was found to exist in an extended, angle-iron shape and in back-folded conformations which were U, J, or helical in shape. The angle-iron and U-shapes were both highly populated conformations with the angle-iron preferred in CHCl3 and the U-shape preferred in H2O. Results for **anandamide** and 2-AG paralleled those for arachidonic acid with the exception that **anandamide** in water does not adopt a pure extended conformation but, rather, favors a hybrid-extended/U-shape. For the dimethyl-heptyl derivative of **anandamide**, the U-shape was found to be predominant in both environments (42% in CHCl3, 38% in H2O), but the population of the angle-iron shape was still significant (25% in CHCl3, 29% in H2O). For all of these ligands, J-shaped conformers constituted from 7% to 17% of the conformer population, while the helical shape was less than 5%. In both CHCl3 and H2O, the presence of the five-membered ring attenuates the ability of PGB2-EA to adopt an extended conformation. PGB2-EA was found instead to exist predominantly in an L-shape (i.e., distorted U-shape). The low probability of PGB2-EA adopting an extended conformation may be why PGB2-EA shows such low affinity for the CB1 receptor. The conformational information obtained here for **anandamide** and 2-AG may be useful in the design of rigid analogs which mimic the preferred mol. conformations (shapes) of these ligands. Such rigid analogs may be useful in deducing the bioactive conformation of these endogenous cannabinoids, not only at the CB receptors but also at the FAAH enzyme active site and possibly at the binding site(s) on the newly proposed **anandamide** transporter.

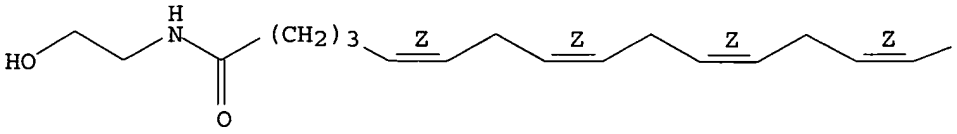
IT **94421-68-8, Anandamide 195612-56-7**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(exploration of biol. relevant conformations of **anandamide**, 2-arachidonylglycerol, and their analogs using conformational memories)

RN 94421-68-8 HCAPLUS

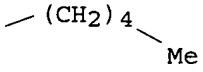
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



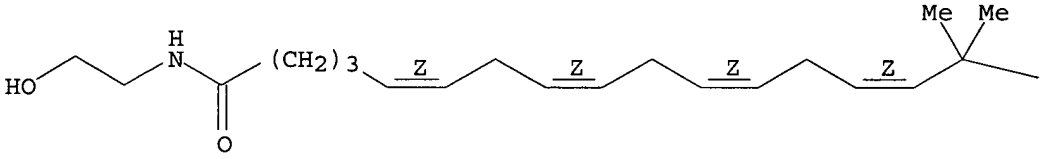
PAGE 1-B



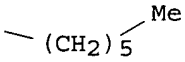
RN 195612-56-7 HCAPLUS
CN 5,8,11,14-Docosatetraenamide, N-(2-hydroxyethyl)-16,16-dimethyl-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



IT **153301-19-0**, **Anandamide** amidohydrolase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ligands for; exploration of biol. relevant conformations of **anandamide**, 2-arachidonylglycerol, and their analogs using conformational memories)
RN 153301-19-0 HCAPLUS
CN Amidase, fatty acid (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:608544 HCAPLUS
DOCUMENT NUMBER: 129:235654
TITLE: Movement of a test substance within a membranous system
INVENTOR(S): Melchior, Donald L.; Makriyannis, Alexandros

PATENT ASSIGNEE(S): University of Massachusetts, USA; University of Connecticut
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9837920	A1	19980903	WO 1998-US3823		19980227 <--
W: AU, CA, JP, KR					
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
AU 9866704	A1	19980918	AU 1998-66704		19980227 <--
PRIORITY APPLN. INFO.:			US 1997-795948	A	19970228
			WO 1998-US3823	W	19980227

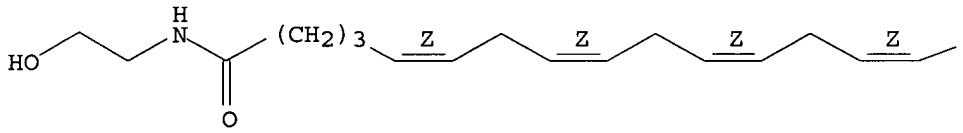
AB A method is disclosed for determining the rate with which a test mol. assocs. with or accumulates in a membrane, by forming a membranous system that contains lipid mols. in association with a reporter mol., applying the test mol. to the system, and measuring the signal generated by the reporter mol. The tests are performed to determine pharmaceuticals mode of action and whether they can be safely and efficiently delivered to the site of action. An example is given for preparation of fluorosomes containing the reporter mol. diphenylhexatriene and phosphatidylcholine as the lipid.

IT **94421-68-8**, **Anandamide 157182-49-5**, AM356
RL: PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(movement of a test substance within a membranous system)

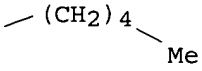
RN 94421-68-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



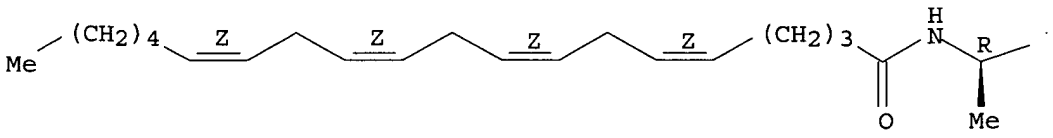
PAGE 1-B



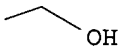
RN 157182-49-5 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-[(1R)-2-hydroxy-1-methylethyl]-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

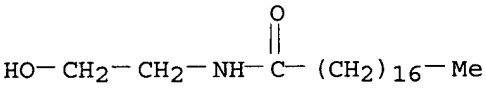
L27 ANSWER 8 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:431578 HCAPLUS
DOCUMENT NUMBER: 129:185235
TITLE: Accumulation of various N-acylethanolamines including N-arachidonoylethanolamine (**anandamide**) in cadmium chloride-administered rat testis
AUTHOR(S): Kondo, Sachiko; Sugimura, Takayuki; Kodaka, Tomoko; Kudo, Naomi; Waku, Keizo; Tokumura, Akira
CORPORATE SOURCE: Fac. Pharmaceutical Sci., Teikyo Univ., Kanagawa, 199-01, Japan
SOURCE: Archives of Biochemistry and Biophysics (**1998**), 354(2), 303-310
CODEN: ABBIA4; ISSN: 0003-9861
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Changes in the levels of various mol. species of N-acylthanolamine in CdCl2-administered rat testis were examined We found that the levels of various N-acylethanolamines including **anandamide** (N-arachidonoylethanolamine), an endogenous cannabinoid receptor ligand, were dramatically increased in CdCl2-administered rat testis. Such changes were particularly prominent for saturated and monoenoic species such as N-palmitoyl species (39-fold at 9 h) and N-stearoyl species (21-fold at 9 h), compared with unsatd. fatty acid-containing species such as **anandamide** (5-fold at 9 h). Noticeably, increased levels were observed of not only N-acylethanolamines but also several species of N-acylphosphatidylethanolamine, potential precursors for N-acylethanolamines. We confirmed that the rat testis microsomal fraction contains phosphodiesterase activity catalyzing the release of N-acylethanolamine from N-acylphosphatidylethanolamine and transacylase activity catalyzing the formation of N-acylphosphatidylethanolamine from phosphatidylethanolamine and phosphatidylcholine. These enzyme activities were not dramatically different in the microsomal fraction obtained from CdCl2-administered rat testis compared with that in the case of control rat testis, at least when estimated in cell-free assay systems, suggesting that the accessibility of the substrates to the enzymes may be increased in CdCl2-administered rat testis to generate a large amount of N-acylethanolamine. Possible pathophysiol. implications of the augmented generation of N-acylethanolamine including **anandamide** in CdCl2-administered rat testis were discussed. (c) 1998 Academic Press.

IT **111-57-9**, N-Stearoylethanolamine **94421-68-8**,

Anandamide
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(accumulation of various acylethanolamines including arachidonoylethanolamine (**anandamide**) in cadmium chloride-administered testis)

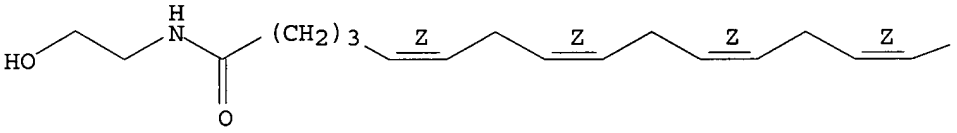
RN 111-57-9 HCAPLUS
CN Octadecanamide, N-(2-hydroxyethyl)- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



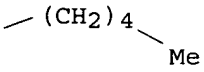
RN 94421-68-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



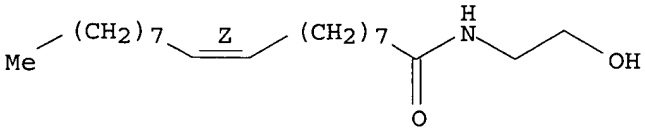
PAGE 1-B



IT **111-58-0**, N-Oleoylethanolamine **68171-52-8**, N-Linoleoylethanolamine **172375-03-0**, N-cis-Vaccenoylethanolamine **211817-55-9**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(accumulation of various acylethanolamines including arachidonoylethanolamine (**anandamide**) in cadmium chloride-administered testis in relation to enzymes)

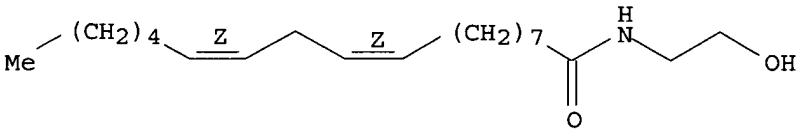
RN 111-58-0 HCAPLUS
CN 9-Octadecenamide, N-(2-hydroxyethyl)-, (9Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



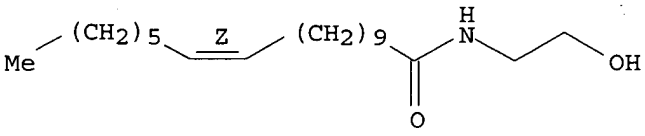
RN 68171-52-8 HCAPLUS
CN 9,12-Octadecadienamide, N-(2-hydroxyethyl)-, (9Z,12Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 172375-03-0 HCAPLUS
CN 11-Octadecenamide, N-(2-hydroxyethyl)-, (11Z)- (9CI) (CA INDEX NAME)

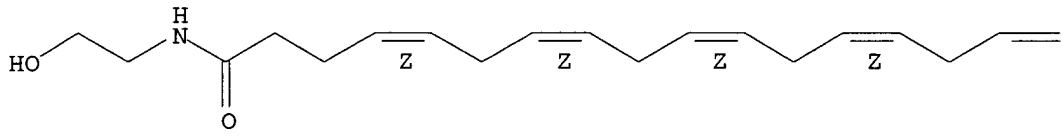
Double bond geometry as shown.



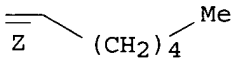
RN 211817-55-9 HCAPLUS
CN 4,7,10,13,16-Docosapentaenamide, N-(2-hydroxyethyl)-, (4Z,7Z,10Z,13Z,16Z)-(9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 9 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:241724 HCAPLUS
DOCUMENT NUMBER: 129:26044
TITLE: The novel endogenous cannabinoid 2-arachidonoylglycerol is inactivated by neuronal- and basophil-like cells: connections with **anandamide**
AUTHOR(S): Di Marzo, Vincenzo; Bisogno, Tiziana; Sugiura, Takayuki; Melck, Dominique; De Petrocellis, Luciano
CORPORATE SOURCE: Istituto per la Chimica di Molecole di Interesse Biologico, Naples, Italy
SOURCE: Biochemical Journal (**1998**), 331(1), 15-19
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press Ltd.

DOCUMENT TYPE: Journal
LANGUAGE: English

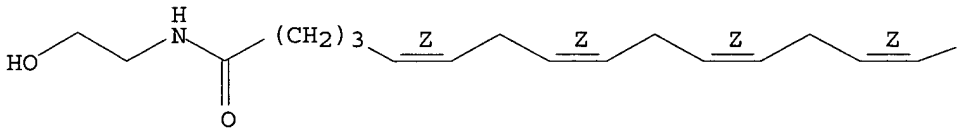
AB The novel endogenous cannabinoid 2-arachidonoylglycerol (2-AG) was rapidly inactivated by intact rat basophilic leukemia (RBL-2H3) and mouse neuroblastoma (N18TG2) cells through diffusion/hydrolysis/reacylation processes. The hydrolysis of 2-AG was inhibited by typical esterase inhibitors and by more specific blockers of "fatty acid amide hydrolase" (FAAH), the enzyme catalyzing the hydrolysis of the other "endocannabinoid", **anandamide** (AEA). No evidence for a facilitated-diffusion process was found. A 2-AG-hydrolyzing activity was detected in homogenates from both cell lines, with the highest levels in membrane fractions. It exhibited an optimal pH at 10, and recognized both 2- and 1(3)- isomers of monoarachidonoylglycerol with similar efficiencies. The apparent Km and Vmax values for [3H]2-AG hydrolysis were 91 μM and 29 μM and 2.4 and 1.8 nmol·min-1·mg of protein-1 resp. in N18TG2 and RBL-2H3 cells. [3H]2-AG hydrolysis was inhibited by Cu2+, Zn2+ and p-hydroxymercuribenzoate, and by 2- or 1(3)-monolinoleoyl- and -linolenoyl-glycerols, but not by the oleoyl, palmitoyl and myristoyl congeners. Purified fractions from solubilized membrane proteins catalyzed, at pH 9.5, the hydrolysis of 2-AG as well as AEA. Accordingly, AEA as well as FAAH inhibitors, including arachidonoyltrifluoromethyl ketone (ATFMK), blocked [3H]2-AG hydrolysis by N18TG2 and RBL-2H3 membranes, whereas 2-AG inhibited [14C]AEA hydrolysis. FAAH blockade by ATFMK preserved from inactivation the 2-AG synthesized de novo by intact N18TG2 cells stimulated with ionomycin. These data suggest that FAAH may be one of the enzymes deputed to the physiol. inactivation of 2-AG, and create intriguing possibilities for the cross-regulation of 2-AG and AEA levels.

IT **94421-68-8, Anandamide**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(arachidonoylglycerol inactivation by neuronal and basophillike cells in relation to)

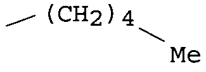
RN 94421-68-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 10 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:36893 HCAPLUS
DOCUMENT NUMBER: 128:175738

TITLE: Application of fluorosome stopped-flow spectrophotometry to monitor the entry of molecules into lipid bilayers
AUTHOR(S): Melchior, D. L.; Makriyannis, A.
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of Massachusetts Medical School, Worcester, MA, 01655, USA
SOURCE: Biotechnology Techniques (**1997**), 11(12), 885-888
CODEN: BTECE6; ISSN: 0951-208X
PUBLISHER: Chapman & Hall
DOCUMENT TYPE: Journal
LANGUAGE: English

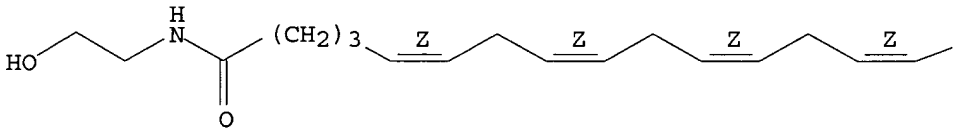
AB A method employing fluorescent unilammelar vesicles was developed for the in vitro determination of non-protein mediated entry rates of mols. into biomembranes with half-times of of entry of from milliseconds to hours. This approach can further determine the equilibrium accumulation and partitioning ratios of test mols. between membranes and delivery solns. or carrier mols.

IT **94421-68-8, Anandamide**
RL: BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); BIOL (Biological study); PROC (Process)
(non-protein mediated membrane uptake of drugs studied by fluorescent spectroscopy)

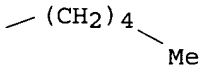
RN 94421-68-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 11 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:12967 HCAPLUS
DOCUMENT NUMBER: 128:152213
TITLE: The sleep-inducing lipid oleamide deconvolutes gap junction communication and calcium wave transmission in glial cells
AUTHOR(S): Guan, Xiaojun; Cravatt, Benjamin F.; Ehring, George R.; Hall, James E.; Boger, Dale L.; Lerner, Richard A.; Gilula, Norton B.
CORPORATE SOURCE: Department of Cell Biology, The Scripps Research

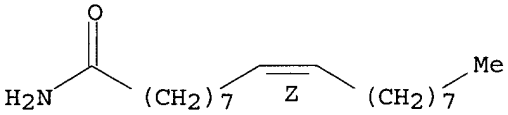
Institute, La Jolla, CA, 92037, USA
SOURCE: Journal of Cell Biology (**1997**), 139(7), 1785-1792
CODEN: JCLBA3; ISSN: 0021-9525
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Oleamide is a sleep-inducing lipid originally isolated from the cerebrospinal fluid of sleep-deprived cats. Oleamide was found to potently and selectively inactivate gap junction-mediated communication between rat glial cells. In contrast, oleamide had no effect on mech. stimulated calcium wave transmission in this same cell type. Other chemical compds. traditionally used as inhibitors of gap junctional communication, like heptanol and 18β-glycyrrhetinic acid, blocked not only gap junctional communication but also intercellular calcium signaling. Given the central role for intercellular small mol. and elec. signaling in central nervous system function, oleamide-induced inactivation of glial cell gap junction channels may serve to regulate communication between brain cells, and in doing so, may influence higher order neuronal events like sleep induction.

IT **301-02-0**, Oleamide
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(oleamide effect on gap junction communication and calcium wave transmission in glial cells)

RN 301-02-0 HCAPLUS
CN 9-Octadecenamide, (9Z)- (9CI) (CA INDEX NAME)

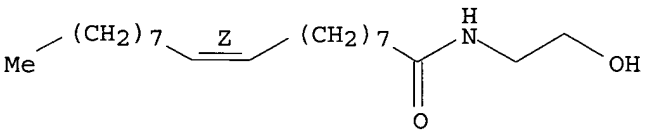
Double bond geometry as shown.



IT **111-58-0 4303-70-2**, trans-9-Octadecenamide
94421-68-8, **Anandamide 117654-34-9**,
cis-11-Octadecenamide **164295-11-8**, cis-8-Octadecenamide
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(oleamide effect on gap junction communication and calcium wave transmission in glial cells in relation to)

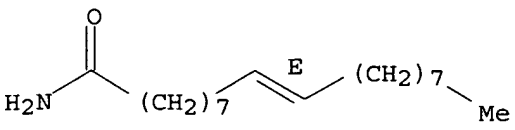
RN 111-58-0 HCAPLUS
CN 9-Octadecenamide, N-(2-hydroxyethyl)-, (9Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 4303-70-2 HCAPLUS
CN 9-Octadecenamide, (9E)- (9CI) (CA INDEX NAME)

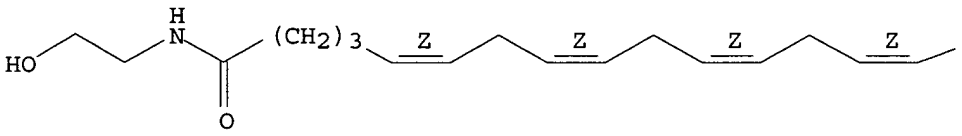
Double bond geometry as shown.



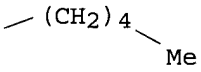
RN 94421-68-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A

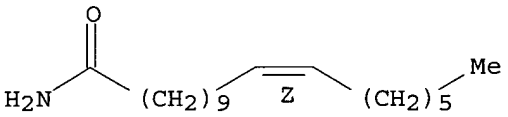


PAGE 1-B



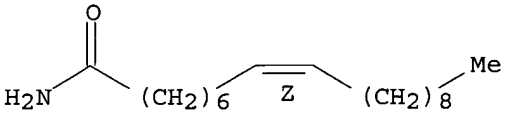
RN 117654-34-9 HCAPLUS
CN 11-Octadecenamide, (11Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 164295-11-8 HCAPLUS
CN 8-Octadecenamide, (8Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 12 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:646545 HCAPLUS
DOCUMENT NUMBER: 127:326920
TITLE: Involvement of a cannabinoid in endothelium-derived hyperpolarizing factor-mediated coronary vasorelaxation
AUTHOR(S): Randall, Michael D.; Kendall, David A.

CORPORATE SOURCE: Department of Physiology and Pharmacology, University of Nottingham Medical School, Queen's Medical Centre, Nottingham, NG7 2UH, UK
SOURCE: European Journal of Pharmacology (**1997**), 335(2/3), 205-209
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors have recently proposed that an endocannabinoid is the endothelium-derived hyperpolarizing factor (EDHF) and have now tested this hypothesis in the rat isolated perfused heart. In this preparation bradykinin gave rise to nitric oxide- and prostanoid-independent relaxations, assessed as redns. in coronary perfusion pressure (ED50 = 14.9 pmol; Rmax = 25.2%), which are thought to be mediated by EDHF. These relaxations were antagonized by both the highly selective cannabinoid antagonist, SR141716A (1 μM) (Rmax = 8.3%) and by the calcium-dependent potassium channel blocker tetrabutylammonium (300 μM) (Rmax = 6.7%) and were abolished by the EDHF inhibitor clotrimazole (3 μM). The endogenous cannabinoid, **anandamide**, similarly caused coronary vasorelaxation (Rmax = 32.3%), which was abolished by clotrimazole (3 μM) and antagonized by both 300 μM tetrabutylammonium (Rmax = 18.2%) and 1 μM SR141716A (Rmax = 16.4%). Accordingly, these results suggest that EDHF-mediated responses in the rat coronary vasculature are due to an endogenous cannabinoid and that **anandamide** causes vasorelaxation through potassium channel activation. These findings are, therefore, consistent with the authors' recent proposal that EDHF is an endogenous cannabinoid.

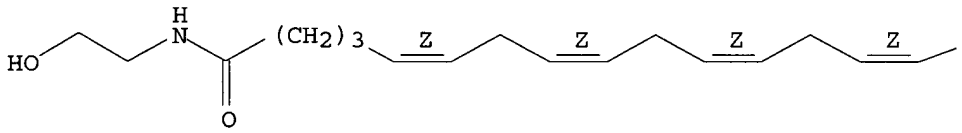
IT **94421-68-8, Anandamide**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(cannabinoid involvement in EDHF-mediated coronary vasorelaxation)

RN 94421-68-8 HCAPLUS

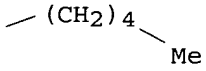
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 13 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:194521 HCAPLUS
DOCUMENT NUMBER: 126:229531

TITLE: The effects of HP-β-CD on aqueous solubility, stability and in vitro corneal penetration of **anandamide**

AUTHOR(S): Jarho, P.; Urtti, A.; Pate, D. W.; Suhonen, P.; Jarvinen, T.

CORPORATE SOURCE: Department of Pharmaceutical Chemistry, University of Kuopio, Kuopio, FIN-70211, Finland

SOURCE: Proceedings of the International Symposium on Cyclodextrins, 8th, Budapest, Mar. 31-Apr. 2, 1996 (**1996**), 395-398. Editor(s): Szejtli, J.; Szente, L. Kluwer: Dordrecht, Neth.
CODEN: 64CDAL

DOCUMENT TYPE: Conference

LANGUAGE: English

AB **Anandamide** (arachidonylethanolamide; AEA), an endogenous ligand for the cannabinoid receptor, has a low aqueous solubility and an instability which hinders its use in aqueous formulations. In the present study, AEA formed an inclusion complex with hydroxypropyl-β-cyclodextrin (HP-β-CD), resulting in greater aqueous solubility and stability of the AEA. The effect of HP-β-CD on corneal penetration of AEA was investigated in vitro by using isolated corneas of rabbits. The complexation of AEA with HP-β-CD increased corneal penetration of AEA compared to a suspension of the compound Maximum permeability was achieved with the lowest HP-β-CD concentration that dissolved the AEA completely. The corneal permeability of AEA correlated well with the concentration of free AEA in solution

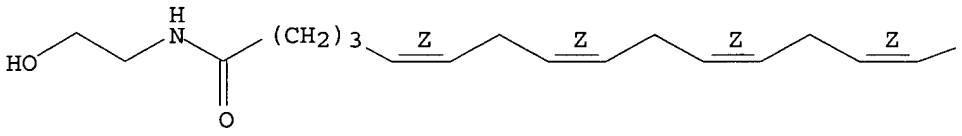
IT **94421-68-8D, Anandamide**, hydroxypropyl β-cyclodextrin complexes
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydroxypropyl β-cyclodextrin on solubility and stability and corneal penetration of **anandamide**)

RN 94421-68-8 HCAPLUS

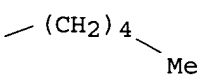
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

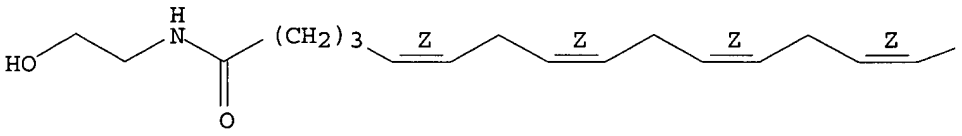


IT **94421-68-8, Anandamide**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(hydroxypropyl β-cyclodextrin on solubility and stability and corneal

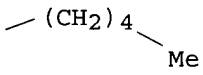
penetration of **anandamide**)
RN 94421-68-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

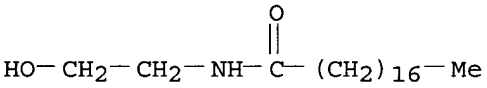


L27 ANSWER 14 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:113597 HCAPLUS
DOCUMENT NUMBER: 126:198536
TITLE: Biosynthesis, uptake, and degradation of **anandamide** and palmitoylethanolamide in leukocytes
AUTHOR(S): Bisogno, Tiziana; Maurelli, Stefano; Melck, Dominique; De Petrocellis, Luciano; Di Marzo, Vincenzo
CORPORATE SOURCE: CNR, Inst. Chimica Molecole Interesse Biologico, Naples, 80072, Italy
SOURCE: Journal of Biological Chemistry (**1997**), 272(6), 3315-3323
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Anandamide** (arachidonoylethanolamide, AnNH) and palmitoylethanolamide (PEA) have been proposed as the physiol. ligands, resp., of central and peripheral cannabinoid receptors. Both of these receptors are expressed in immune cells, including macrophages and mast cells/basophils, where immunomodulatory and/or anti-inflammatory actions of AnNH and PEA have been recently reported. The authors now provide biochem. grounds to these actions by showing that the biosynthesis, uptake, and degradation of AnNH and PEA occur in leukocytes. On stimulation with ionomycin, J774 macrophages and RBL-2H3 basophils produced AnNH and PEA, probably through the hydrolysis of the corresponding N-acylphosphatidylethanolamines, also found among endogenous phospholipids. Immunol. challenge of RBL-2H3 cells also caused AnNH and PEA release. The chemical structure and the amts. of AnNH and PEA produced upon ionomycin stimulation were determined by double radiolabeling expts. and isotope dilution gas chromatog./electron impact mass spectrometry. Both cell lines rapidly sequestered the two amides from the culture medium through temperature-dependent, saturable and chemical inactivable mechanisms. Once taken up by basophils, AnNH and PEA compete for the same inactivating enzyme

which catalyzes their hydrolysis to ethanolamine. This enzyme was found in both microsomal and 10,000 + g fractions of RBL cell homogenates, and exhibited similar inhibition and temperature/pH dependence profiles but a significantly higher affinity for PEA with respect to neuronal " **anandamide** amidohydrolase". The finding of biosynthetic and inactivating mechanisms for AnNH and PEA in macrophages and basophils supports the previously proposed role as local modulators of immune/inflammatory reactions for these two long chain acylethanolamides.

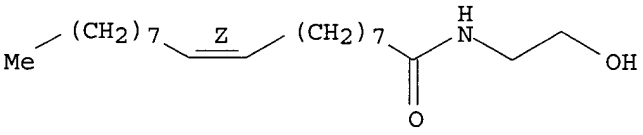
IT **111-57-9 111-58-0 57086-93-8**
68171-52-8
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(acylethanolamide metabolism in leukocytes)

RN 111-57-9 HCAPLUS
CN Octadecanamide, N-(2-hydroxyethyl)- (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



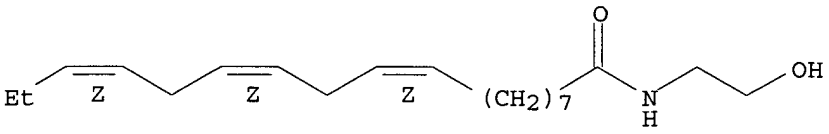
RN 111-58-0 HCAPLUS
CN 9-Octadecenamide, N-(2-hydroxyethyl)-, (9Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



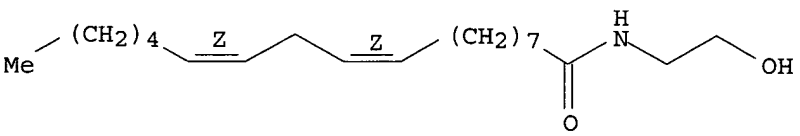
RN 57086-93-8 HCAPLUS
CN 9,12,15-Octadecatrienamide, N-(2-hydroxyethyl)-, (9Z,12Z,15Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 68171-52-8 HCAPLUS
CN 9,12-Octadecadienamide, N-(2-hydroxyethyl)-, (9Z,12Z)- (9CI) (CA INDEX NAME)

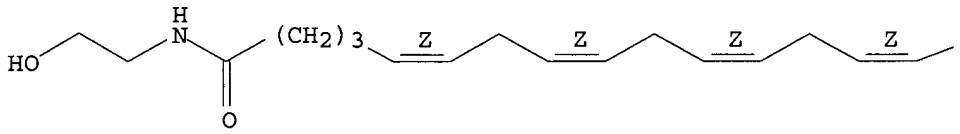
Double bond geometry as shown.



IT **94421-68-8**, Arachidonylethanolamide
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(biosynthesis, uptake, and degradation of **anandamide** and palmitoylethanolamide in leukocytes)
RN 94421-68-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



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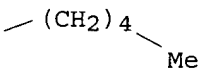
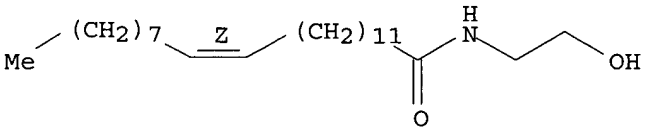


IT **18190-74-4 187762-46-5 187762-47-6 187762-48-7**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(fatty acid ethanolamide hydrolase specificity in leukocytes)
RN 18190-74-4 HCAPLUS
CN 13-Docosenamide, N-(2-hydroxyethyl)-, (13Z)- (9CI) (CA INDEX NAME)

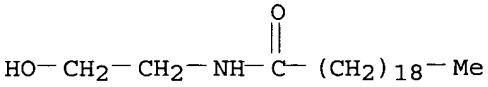
Double bond geometry as shown.



RN 187762-46-5 HCAPLUS
CN Eicosadienamide, N-(2-hydroxyethyl)-, (Z,Z)- (9CI) (CA INDEX NAME)

CM 1

CRN 94421-69-9
CMF C22 H45 N O2



RN 187762-47-6 HCAPLUS
CN Eicosenamide, N-(2-hydroxyethyl)-, (Z)- (9CI) (CA INDEX NAME)

CM 1

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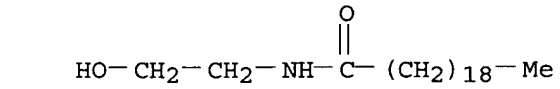
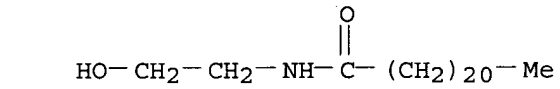
CMF C22 H45 N O2



RN 187762-48-7 HCAPLUS
CN Docosahexaenamide, N-(2-hydroxyethyl)-, (all-Z)- (9CI) (CA INDEX NAME)

CM 1

CRN 94109-05-4
CMF C24 H49 N O2



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

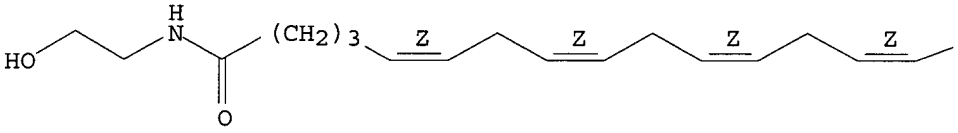
L27 ANSWER 15 OF 15 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:399889 HCAPLUS
DOCUMENT NUMBER: 125:95827
TITLE: Increase in aqueous solubility, stability and in vitro corneal permeability of **anandamide** by hydroxypropyl-β-cyclodextrin
AUTHOR(S): Jarho, Pekka; Urtti, Arto; Pate, David W.; Suhonen, Pekka; Jaervinen, Tomi
CORPORATE SOURCE: Department of Pharmaceutical Chemistry, University of Kuopio, P.O. Box 1627, FIN-70211, Kuopio, Finland
SOURCE: International Journal of Pharmaceutics (**1996**), 137(2), 209-216
CODEN: IJPHDE; ISSN: 0378-5173
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Arachidonylethanolamide (AEA), an endogenous ligand for the cannabinoid receptor, has a low aqueous solubility and an instability which hinder its use in aqueous formulations. In the present study, the effect of cyclodextrins (CDs) on the aqueous solubility, stability and in vitro corneal permeability of AEA was studied. The corneal penetration of AEA in HP-β-CD formulations was investigated in vitro by using isolated corneas of rabbits. The phase solubility diagram with HP-β-CD was classified as Ap-type and stability consts. (K1:1 and K1:2) for 1:1 and 1:2 inclusion complexes were calculated to be 39 419 M-1 and 12 M-1, resp. The phase solubility diagram of AEA with DIME-β-CD and HP-β-CD were of the AL-type, indicating the formation of 1:1-complexes. The stability consts. for 1:1-complexes were

744,877M-1 and 15,469M-1, resp. The complexation of AEA with HP-β-CD markedly increased the stability of AEA. The shelf-life (t90%) of AEA in 10.0% HP-β-CD solution at 50° was determined to be 166 days. The complexation of AEA with HP-β-CD increased corneal penetration of AEA compared to a suspension of the compound Maximum permeability was achieved with the lowest HP-β-CD concentration that dissolved AEA completely. The permeability of AEA correlated well with the concentration of free AEA in solution

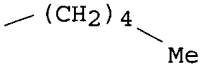
IT **94421-68-8DP**, **Anandamide**, β-cyclodextrin ether complexes
RL: BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(stability and solubility and corneal permeability enhancement of **anandamide** by hydroxypropyl-β-cyclodextrin)
RN 94421-68-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



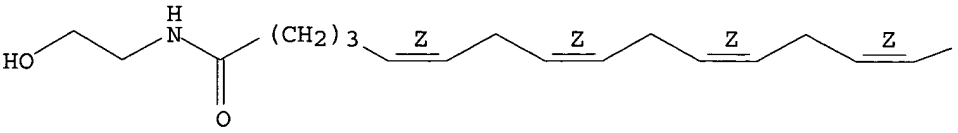
PAGE 1-B

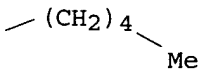


IT **94421-68-8**, **Anandamide**
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(stability and solubility and corneal permeability enhancement of **anandamide** by hydroxypropyl-β-cyclodextrin)
RN 94421-68-8 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A





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=> => fil reg
FILE 'REGISTRY' ENTERED AT 14:49:01 ON 14 FEB 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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provided by InfoChem.

STRUCTURE FILE UPDATES:   13 FEB 2006  HIGHEST RN 874180-50-4
DICTIONARY FILE UPDATES:  13 FEB 2006  HIGHEST RN 874180-50-4

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

*********************************************************************
*                                                                   *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,   *
* effective March 20, 2005.  A new display format, IDERL, is now    *
* available and contains the CA role and document type information. *
*                                                                   *
*********************************************************************

Structure search iteration limits have been increased.  See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> d stat que
L28           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "ARACHIDONIC ACID"/CN
L29           1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "2,2-DIMETHYLARACHIDONIC
                ACID"/CN
L30           2 SEA FILE=REGISTRY ABB=ON  PLU=ON  L28 OR L29


=> d ide can l30 1-2

L30  ANSWER 1 OF 2  REGISTRY  COPYRIGHT 2006 ACS on STN
RN   60839-73-8  REGISTRY
ED   Entered STN:  16 Nov 1984
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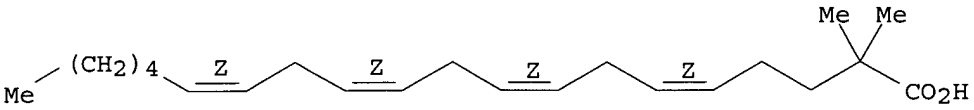
CN 5,8,11,14-Eicosatetraenoic acid, 2,2-dimethyl-, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5,8,11,14-Eicosatetraenoic acid, 2,2-dimethyl-, (all-Z)-
OTHER NAMES:
CN **2,2-Dimethylarachidonic acid**
FS STEREOSEARCH
MF C22 H36 O2
LC STN Files: BEILSTEIN*, BIOSIS, CA, CAPLUS, CASREACT, IFICDB, IFIPAT, IFIUDB, USPATFULL
(*File contains numerically searchable property data)

Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

8 REFERENCES IN FILE CA (1907 TO DATE)
8 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:179906

REFERENCE 2: 135:137336

REFERENCE 3: 93:25952

REFERENCE 4: 92:146280

REFERENCE 5: 89:108181

REFERENCE 6: 88:152049

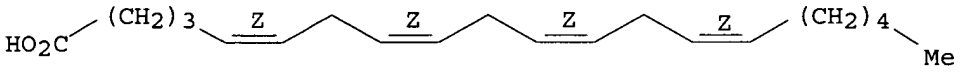
REFERENCE 7: 88:152043

REFERENCE 8: 85:159441

L30 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2006 ACS on STN
RN 506-32-1 REGISTRY
ED Entered STN: 16 Nov 1984
CN 5,8,11,14-Eicosatetraenoic acid, (5Z,8Z,11Z,14Z)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5,8,11,14-Eicosatetraenoic acid, (all-Z)- (8CI)
OTHER NAMES:
CN (all-Z)-5,8,11,14-Eicosatetraenoic acid
CN 5,8,11,14-all-cis-Eicosatetraenoic acid
CN 5-cis,8-cis,11-cis,14-cis-Eicosatetraenoic acid
CN 5Z,8Z,11Z,14Z-Eicosatetraenoic acid
CN all-cis-5,8,11,14-Eicosatetraenoic acid
CN arachidonate
CN **Arachidonic acid**
CN cis-Δ5,8,11,14-Eicosatetraenoic acid
FS STEREOSEARCH
DR 10417-93-3, 929-92-0
MF C20 H32 O2

CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CABA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIOGENES, DRUGU, EMBASE, GMELIN*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, NAPRALERT, NIOSHTIC, PATDPASPC, PROMT, RTECS*, SPECINFO, TOXCENTER, USPAT2, USPATFULL, VETU, VTB
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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2305 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
29925 REFERENCES IN FILE CAPLUS (1907 TO DATE)
132 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 144:130571

REFERENCE 2: 144:129184

REFERENCE 3: 144:128765

REFERENCE 4: 144:128229

REFERENCE 5: 144:128228

REFERENCE 6: 144:128227

REFERENCE 7: 144:128152

REFERENCE 8: 144:128095

REFERENCE 9: 144:128058

REFERENCE 10: 144:127828

=> e anandamide/cn
E1 1 ANANASOSIDE B/CN
E2 1 ANANDAMIDASE/CN
E3 1 --> ANANDAMIDE/CN
E4 1 ANANDAMIDE AMIDASE/CN
E5 1 ANANDAMIDE AMIDOHYDROLASE/CN
E6 1 ANANDAMIDE AMIDOHYDROLASE (SUS SCROFA)/CN
E7 1 ANANDAMIDE HYDROLASE/CN
E8 2 ANANDAMIDE SYNTHASE/CN
E9 3 ANANDITE/CN
E10 1 ANANDITE (BA(FE0.5-1MG0-0.5)3(SI3FE)((OH)S)O10)/CN

```
E11          1     ANANDITE-1M/CN
E12          1     ANANDITE-1M (BA(FE0.5-1MG0-0.5)3(SI3FE)((OH)S)O10)/CN

=> s e3
L31          1 ANANDAMIDE/CN

=> d ide can

L31  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2006 ACS on STN
RN   94421-68-8  REGISTRY
ED   Entered STN:  26 Jan 1985
CN   5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (5Z,8Z,11Z,14Z)- (9CI)
     (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   5,8,11,14-Eicosatetraenamide, N-(2-hydroxyethyl)-, (all-Z)-
OTHER NAMES:
CN   Anandamide
CN   Arachidonylethanolamide
CN   N-(2-Hydroxyethyl)arachidonamide
CN   N-(2-Hydroxyethyl)arachidonylamide
CN   N-Arachidonoylethanolamide
CN   N-Arachidonylethanolamine
FS   STEREOSEARCH
MF   C22 H37 N O2
CI   COM
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BIOSIS, BIOTECHNO, CA,
       CAPLUS, CASREACT, CHEMCATS, CIN, CSCHEM, EMBASE, IPA, MEDLINE, MRCK*,
       PHAR, PROMT, PROUSDDR, RTECS*, TOXCENTER, USPAT2, USPATFULL
         (*File contains numerically searchable property data)

Double bond geometry as shown.
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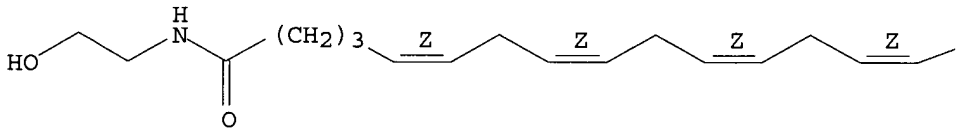
PAGE 1-A



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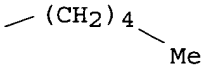


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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

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              29 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
            1167 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE   1:  144:126790

REFERENCE   2:  144:124391

REFERENCE   3:  144:121562
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REFERENCE 5: 144:121209

REFERENCE 6: 144:101306

REFERENCE 7: 144:81209

REFERENCE 8: 144:64548

REFERENCE 9: 144:64435

REFERENCE 10: 144:64266

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6/29/04